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Toxaphene: Ambient Water Quality Criteria

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TOXAPHENE

Ambient Water Quality Criteria

Criteria and Standards Division
Office of Water Planning and Standards
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Section 304(a) of the Clean Water Act (33 U.S.C. 1314(a)), requires EPA to publish and periodically update water quality criteria. These criteria are to reflect the latest scientific knowledge on the identifiable effects of pollutants on public health and welfare, aquatic life, and recreation. This report presents water quality criteria for toxaphene. It presents concentration criteria for the protection of fresh water and saltwater aquatic life. It presents 'safe' concentrations for humans, and in the case of suspect or proven carcinogens, gives various levels of incremental cancer risk. A section 304(a) water quality criterion is a qualitative or quantitative estimate of the concentration of a water constituent or pollutant in ambient waters which, when not exceeded, will ensure a water quality sufficient to protect a specified water use. Under the Act a criterion is a scientific entity, based solely on data and scientific judgement. It does not reflect consi....

KEYWORDS: *Water quality, *Toxicology, *Toxic substances, *Water pollution effects(Humans), *Toxaphene.

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CRITERION DOCUMENT

TOXAPHENE

CRITERIA

Aquatic Life

For toxaphene the criterion to protect freshwater aquatic life as derived using the Guidelines is 0.007 µg/l as a 24-hour average and the concentration should not exceed 0.47 µg/l at any time.

For toxaphene the criterion to protect saltwater aquatic life as derived using the Guidelines is 0.019 µg/l as a 24-hour average and the concentration should not exceed 0.12 µg/l at any time.

Human Health

For the maximum protection of human health from the potential carcinogenic effects of exposure to toxaphene through ingestion of water and contaminated aquatic organisms, the ambient water concentration is zero. Concentrations of toxaphene estimated to result in additional lifetime cancer risks ranging from no additional risk to an additional risk of 1 in 100,000 are presented in the Criterion Formulation section of this document. The Agency is considering setting criteria at an interim target risk level in the range of 10^{-5}, 10^{-6}, or 10^{-7} with corresponding criteria of 4.7×10^{-4} µg/l, 4.7×10^{-5} µg/l, and 4.7×10^{-6} µg/l, respectively.

Introduction

Toxaphene is a commercially produced, broad spectrum, chlorinated hydrocarbon pesticide consisting primarily of chlorinated camphene and a mixture of related compounds and isomers. It was introduced in the United States in 1948 as a contact insecticide under various trade names and is currently the most heavily used insecticide in the United States, having replaced many of the agricultural applications of DDT, for which registration has been cancelled. Annual production of toxaphene exceeds 100 million pounds, with primary usage in agricultural crop application, mainly cotton.

Toxaphene has demonstrated carcinogenic effects in laboratory animals. In addition, toxaphene is highly toxic to many aquatic invertebrate and vertebrate species and has been shown to cause the "broken back syndrome" in fish fry. These observations, together with reported bioconcentration factors as high as 91,000 indicate that toxaphene poses a threat to living organisms, particularly in the aquatic environment. On May 25, 1977, the U.S. Environmental Protection Agency issued a notice of rebuttable presumption against registration and continued registration of pesticide products containing toxaphene.

Toxaphene is a complex mixture of polychlorinated camphenes and bornanes with the typical empirical formula $C_{10}H_{10}Cl_8$ and an average molecular weight of 414. It is an amber, waxy solid with a mild terpene odor, a melting

point range of 65 to 90°C, a vapor pressure 0.17 to 0.40 mm Hg at 25°C, and a density of 1.64 at 25°C (Brooks, 1974; Metcalf, 1966). Toxaphene has a solubility in water of approximately 0.4 to 3.0 mg/l and is readily soluble in relatively nonpolar solvents, with an octanol/water partition coefficient of 825 (Brooks, 1974; Edwards, 1973; Metcalf, 1966; Sanborn, et al. 1976). Paris, et al. (1977) reported a toxaphene partition coefficient value of 3,300. Gas chromatographic analysis suggests the presence of approximately 177 components in technical toxaphene (Holmstead, et al. 1974). Infrared absorptivity at 7.2 microns aids in distinguishing toxaphene from other chlorinated terpene products such as strobane. Although tricyclene may accompany the camphene, the commercial mixture contains less than five percent of other terpenes.

Toxaphene is commercially produced by reacting camphene with chlorine in the presence of ultraviolet radiation and certain catalysts to yield chlorinated camphene with a chlorine content of 67 to 69 percent (Metcalf, 1966). The chlorine content of the commercial product is limited to this narrow range since the insecticidal activity peaks sharply at those percentage levels. Toxaphene is available in various formulations as an emulsifiable concentrate, wettable powder, or dust.

The commercial product is relatively stable but may dehydrochlorinate upon prolonged exposure to sunlight, alkali, or temperatures above 120°C (Metcalf, 1966; Brooks, 1974).

When dispersed in natural water systems, toxaphene tends to be adsorbed by the particulates present or to be taken up by living organisms and bioconcentrated. Thus, it is seldom found at high levels as a soluble component in receiving waters but can persist in sediments or remain adsorbed on suspended solids for prolonged periods.

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AQUATIC LIFE TOXICOLOGY*

FRESHWATER ORGANISMS

Introduction

Toxaphene has been used as an insecticide for many years. At one time toxaphene was used as a fish erraticant and there are early acute static test data on the toxicity of toxaphene which showed it to be very toxic to freshwater fish (Henderson, 1959; Katz, 1961).

Chronic data were published recently for both fish and invertebrate species. Data for bioconcentration were obtained from the fish chronic exposures but there are no appropriate invertebrate bioconcentration data.

The effect on aquatic plants is not known but probably is not important since this chemical is formulated as an insecticide and not as a herbicide.

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*The reader is referred to the Guidelines for Deriving Water Quality Criteria for the Protection of Aquatic Life [43 FR 21506 (May 18, 1978) and 43 FR 29028 (July 5, 1978)] in order to better understand the following discussion and recommendation. The following tables contain the appropriate data that were found in the literature, and at the bottom of each table are the calculations for deriving various measures of toxicity as described in the Guidelines.

Acute Toxicity

As shown in Table 1, 52 96-hour LC50 values are available for 18 species of fish. Four of the 52 LC50 values are from flow-through tests and the rest are from static tests. Johnson and Julin (In press) showed that exposures of bluegills and channel catfish to toxaphene in flow-through test systems did not produce an appreciable increase in toxicity over static test systems. However, fathead minnows were three times more susceptible to toxaphene poisoning in the flow-through system (Johnson and Julin, In press).

Unadjusted LC50 values ranged from 0.8 to 28 µg/l for the 18 species of fish listed in Table 1. No single species appeared uniquely sensitive or resistant. When the geometric mean of all values in Table 1 is divided by the sensitivity factor (3.9) the LC50 value calculated (0.92 µg/l) is higher than one value in Table 1. That value (0.8 µg/l) is for channel catfish swim-up fry at 25° C, suggesting a very reasonable fit of the data to the procedures in the Guidelines. The Final Fish Acute Value is 0.92 µg/l.

The data base for invertebrate species (Table 2) contains 17 data points for 13 species; six species represent rather different decapods and insects. There are no toxicity data with flowthrough test procedures. The range of species sensitivity displayed in Table 2 (the highest LC50 value divided by the lowest is large, 178. The geometric mean of the invertebrate LC50 data is 9.6 µg/l. When the geometric mean is divided by the sensitivity factor (21), a value of 0.46 µg/l becomes the Final Invertebrate Acute Value. The lowest LC50 value is 1.1 µg/l which is 2.4 times the Final Invertebrate Acute Value.

Since the Final Invertebrate Acute Value of 0.46 µg/l is lower than the Final Fish Acute Value of 0.92 µg/l, the Final Acute Value for freshwater aquatic life is 0.46 µg/l.

Chronic Toxicity

There are two chronic test values for fathead minnows and channel catfish (Table 3). A third chronic test result with brook trout is in Table 6 because even at the lowest concentration tested (0.039 µg/l) there was an effect on growth. The geometric mean of the chronic values is 0.047 µg/l which is 77 times lower than the geometric mean acute value for fish. The chronic value divided by the sensitivity factor (6.7) from the Guidelines gives a 95 percent species protection concentration of 0.007 µg/l. A different method of estimating the same value is obtained by multiplying the Final Fish Acute Value by the application factor calculated from the chronic data. This estimate is 0.018 µg/l, about 2 1/2 times larger. This suggests the Guideline sensitivity factor is reasonable for fish chronic toxicity. The Final Fish Chronic Value is the lowest of the three estimates in Table 3 or 0.007 µg/l.

Chronic data for invertebrate species are in Table 4. Chronic values for three species vary by a factor of 20, indicating the sensitivity difference between the tested species. Daphnia magna was the most sensitive of the three species. The chronic value divided by the sensitivity factor (5.1) from the Guidelines gives a 95 percent species protection concentration of 0.06 µg/l. This value is lower than the lowest chronic value of 0.09 µg/l, and 0.06 µg/l becomes the Final Invertebrate Chronic Value.

Plant Effects

No data for plant effects were found.

Residues

Table 5 contains equilibrium bioconcentration data for three species of fish. The geometric mean of the bioconcentration factors is 44,000. A residue limit for consumers of aquatic life, established by the U.S. Food and Drug Administration is 0.5 mg/kg in animal feed. Fish meal is used in domestic animal feed and the 0.5 mg/kg value is used to calculate a Residue Limited Toxicant Concentration (RLTC) value. By dividing the FDA limit of 0.5 mg/kg by the bioconcentration factor of 44,000 a RLTC value of 0.011 µg/l is obtained. The Final Fish Chronic Value (0.007 µg/l), Final Invertebrate Chronic Value (0.06 µg/l), Final Plant Value (no data) and the RLTC Value (0.011 µg/l) are the values derived to protect aquatic life and the consumer of aquatic life. The lowest value is the Final Fish Chronic Value and this becomes the Final Chronic Value.

Miscellaneous

Table 6 contains no data that would alter the selection of 0.007 µg/l for the Final Chronic Value.

CRITERION FORMULATION

Freshwater-Aquatic Life

Summary of Available Data

The concentrations below have been rounded to two significant figures.

Final Fish Acute Value = 0.92 µg/l

Final Invertebrate Acute Value = 0.46 µg/l

Final Acute Value = 0.47 µg/l

Final Fish Chronic Value = 0.007 µg/l

Final Invertebrate Chronic Value = 0.06 µg/l

Final Plant Value = not available

Residue Limited Toxicant Concentration = 0.011 µg/l

Final Chronic Value = 0.007 µg/l

0.44 x Final Acute Value = 0.20 µg/l

The maximum concentration of toxaphene is the Final Acute Value of 0.47 µg/l and the 24-hour average concentration is the Final Chronic Value of 0.007 µg/l. No important adverse effects on freshwater aquatic organisms have been reported to be caused by concentrations lower than the 24-hour average concentration.

CRITERION: For toxaphene the criterion to protect freshwater aquatic life as derived using the Guidelines is 0.007 µg/l as a 24-hour average and the concentration should not exceed 0.47 µg/l at any time.

Table 1. Freshwater fish acute values for toxaphene

Organism	Bioassay Method*	Test Conc.**	Time (hrs)	LC50 (ug/l)	Adjusted LC50 (ug/l)	Reference
Coho salmon, Oncorhynchus kisutch	S	U	96	9.4	5.1	Katz, 1961
Coho salmon, Oncorhynchus kisutch	S	U	96	8	4.4	Macek & McAllister, 1970
Chinook salmon, Oncorhynchus tshawytcha	S	U	96	2.5	1.4	Katz, 1961
Rainbow trout, Salmo gairdneri	S	U	96	8.4	4.6	Katz, 1961
Rainbow trout, Salmo gairdneri	S	U	96	8.4	4.6	Mahdi, 1966
Rainbow trout, Salmo gairdneri	S	U	96	5.4	3.0	Cope, 1965
Rainbow trout, Salmo gairdneri	S	U	96	2.7	1.5	Cope, 1965
Rainbow trout, Salmo gairdneri	S	U	96	1.8	0.98	Cope, 1965
Rainbow trout, Salmo gairdneri	S	U	96	11	6.0	Macek & McAllister, 1970
Brown trout, Salmo trutta	S	U	96	3	1.6	Macek & McAllister, 1970
Brook trout, Salvelinus fontinalis	FT	M	96	10.8	10.8	Mayer, et al. 1975
Stoneroller, Campostoma anomalum	S	U	96	14	7.7	Mahdi, 1966
Goldfish, Carassius auratus	S	U	96	5.6	3.1	Henderson, et al. 1959
Goldfish, Carassius auratus	S	U	96	28	15	Mahdi, 1966
Goldfish, Carassius auratus	S	U	96	14	7.7	Macek & McAllister, 1970

Table 1. (Continued)

Organism	Bioassay Method*	Test Conc.**	Time (hrs)	LC50 (ug/l)	Adjusted LC50 (ug/l)	Reference
Carp, Cyprinus carpio	S	U	96	4	2.2	Macek & McAllister, 1970
Golden shiner, Notemigonus crysoleucas	S	U	96	6	3.3	Mahdi, 1966
Bluntnose minnow, Pimephales notatus	S	U	96	6.3	3.4	Mahdi, 1966
Fathead minnow, Pimephales promelas	S	U	96	7.5	4.1	Henderson, et al. 1959
Fathead minnow, Pimephales promelas	S	U	96	5.1	2.8	Henderson, et al. 1959
Fathead minnow, Pimephales promelas	S	U	96	14	7.7	Macek & McAllister, 1970
Fathead minnow, Pimephales promelas	S	U	96	13	7.1	Cohen, et al. 1960
Fathead minnow, Pimephales promelas	S	U	96	20	11	Johnson & Julin, In press
Fathead minnow, Pimephales promelas	FT	U	96	7	5.4	Johnson & Julin, In press
Black bullhead, Ictalurus melas	S	U	96	1.8	0.98	Mahdi, 1966
Black bullhead, Ictalurus melas	S	U	96	5	2.7	Macek & McAllister, 1970
Channel catfish, Ictalurus punctatus	S	U	96	13	7.1	Macek & McAllister, 1970
Channel catfish, Ictalurus punctatus	FT	U	96	5.5	4.2	Johnson & Julin, In press
Channel catfish, Ictalurus punctatus	S	U	96	2.8	1.5	Johnson & Julin, In press
Channel catfish, Ictalurus punctatus	S	U	96	0.8	0.44	Johnson & Julin, In press

Table 1. (Continued)

Organism	Bioassay Method*	Test Conc.**	Time (hrs)	LC50 (ug/l)	Adjusted LC50 (ug/l)	Reference
Channel catfish, Ictalurus punctatus	S	U	96	4.7	2.6	Johnson & Julin, In press
Channel catfish, Ictalurus punctatus	S	U	96	4.2	2.3	Johnson & Julin, In press
Channel catfish, Ictalurus punctatus	S	U	96	3.7	2.0	Johnson & Julin, In press
Channel catfish, Ictalurus punctatus	S	U	96	2.7	1.5	Johnson & Julin, In press
Channel catfish, Ictalurus punctatus	S	U	96	3.4	1.9	Johnson & Julin, In press
Channel catfish, Ictalurus punctatus	S	U	96	3.0	1.6	Johnson & Julin, In press
Channel catfish, Ictalurus punctatus	S	U	96	3.9	2.1	Johnson & Julin, In press
Channel catfish, Ictalurus punctatus	S	U	96	3.2	1.7	Johnson & Julin, In press
Channel catfish, Ictalurus punctatus	S	U	96	3.9	2.1	Johnson & Julin, In press
Channel catfish, Ictalurus punctatus	S	U	96	4.7	2.6	Johnson & Julin, In press
Mosquitofish, Gambusia affinis	S	U	96	8	4.4	Chatyarach, et al. 1975
Guppy, Lebistes reticulatus	S	U	96	20	11	Henderson, et al. 1959
Bluegill, Lepomis macrochirus	S	U	96	3.2	1.7	Macek, et al. 1969
Bluegill, Lepomis macrochirus	S	U	96	2.6	1.4	Macek, et al. 1969
Bluegill, Lepomis macrochirus	S	U	96	2.4	1.3	Macek, et al. 1969

Table 1. (Continued)

Organism	Bioassay Method*	Test Conc.**	Time (hrs)	LC50 (ug/l)	Adjusted LC50 (ug/l)	References
Bluegill, Lepomis macrochirus	S	U	96	3.5	1.9	Henderson, et al. 1959
Bluegill, Lepomis macrochirus	S	U	96	18	9.8	Macek & McAllister, 1970
Bluegill, Lepomis macrochirus	S	U	96	2.4	1.3	Johnson & Julin, In press
Bluegill, Lepomis macrochirus	FT	U	96	3.4	2.6	Johnson & Julin, In press
Redear sunfish, Lepomis microlophus	S	U	96	13	7.1	Macek & McAllister, 1970
Largemouth bass, Micropterus salmoides	S	U	96	2	1.1	Macek & McAllister, 1970
Yellow perch, Perca flavescens	S	U	96	12	6.6	Macek & McAllister, 1970

* S = static, FT = flow-through

** U = unmeasured, M = measured

Geometric mean of adjusted values = 3.6 µg/l $\quad \frac{3.6}{3.9} = 0.92$ µg/l

Lowest value from a flow-through test with measured concentrations = 10.8 µg/l

Table 2. Freshwater invertebrate acute values for toxaphene

Organism	Bioassay Method*	Test Conc.**	Time (hrs)	LC50 (ug/l)	Adjusted LC50 (ug/l)	Reference
Cladoceran, *Simocephalus serrulatus*	S	U	48	19	6.9	Sanders & Cope, 1966
Cladoceran, *Simocephalus serrulatus*	S	U	48	10	3.6	Sanders & Cope, 1966
Cladoceran, *Daphnia pulex*	S	U	48	15	5.5	Sanders & Cope, 1966
Cladoceran, *Daphnia magna*	S	U	48	10	3.6	Sanders, In press
Scud, *Gammarus lacustris*	S	U	96	26	22	Sanders, 1969
Scud, *Gammarus fasciatus*	S	U	96	35	30	Sanders, 1972
Scud, *Gammarus fasciatus*	S	U	96	6	5.1	Sanders, 1972
Scud, *Gammarus pseudolimnaeus*	S	U	96	24	20	Sanders, In press
Glass shrimp, *Palaemonetes kadiakensis*	S	U	96	36	30	Chaiyarach, et al. 1975
Glass shrimp, *Palaemonetes kadiakensis*	S	U	96	28	24	Sanders, 1972
Glass shrimp, *Palaemonetes kadiakensis*	S	U	24	21	4.6	Naqvi & Ferguson, 1970
Crayfish, *Procambarus simulans*	S	U	96	210	178	Chaiyarach, et al. 1975
Crayfish, *Procambarus acutus*	S	U	48	61	22	Albaugh, 1972
Midge (larva), *Chironomus plumosus*	S	U	48	180	66	Sanders, In press
Stonefly, *Pteronarcys californica*	S	U	96	2.3	1.9	Sanders & Cope, 1968

Table 2. (Continued)

Organism	Bioassay Method*	Test Conc.**	Time (hrs)	LC50 (ug/l)	Adjusted LC50 (ug/l)	Reference
Stonefly, Pteronarcella badia	S	U	96	3.0	2.5	Sanders & Cope, 1968
Stonefly, Claassenia sabulosa	S	U	96	1.3	1.1	Sanders & Cope, 1968

* S = static

** U = unmeasured

Geometric mean of adjusted values = 9.6 ug/l $\frac{9.6}{21} = 0.46$ ug/l

Table 3. Freshwater fish chronic values for toxaphene (Mayer, et al. 1977)

Organism	Test*	Limits (ug/l)	Chronic Value (ug/l)
Fathead minnow, Pimephales promelas	LC	0.025-0.054	0.037
Channel catfish, Ictalurus punctatus	LC	0.049-0.072	0.059

* LC = life cycle or partial life cycle

Geometric mean of chronic values = 0.047 µg/l $\quad \frac{0.047}{6.7} = 0.007$ µg/l

Lowest chronic value = 0.037 µg/l

Application Factor Values (Mayer, et al. 1977)

Organism	96-hr LC50 (µg/l)	MATC (µg/l)	AF
Fathead minnow, Pimephales promelas	7	0.037	0.0053
Channel catfish, Ictalurus punctatus	5.5	0.059	0.011

Geometric mean AF = 0.0076 $\quad$ Geometric mean LC50 = 6.2 µg/l

$0.0076 \sqrt{0.92 \text{ µg/l} \times 6.2 \text{ µg/l}} = 0.018$ µg/l

Table 4. Freshwater invertebrate chronic values for toxaphene

Organism	Test*	Limits (ug/l)	Chronic Value (ug/l)	Reference
Cladoceran, *Daphnia magna*	LC	0.07-0.12	0.09	Sanders, In press
Scud, *Gammarus pseudolimnaeus*	LC	0.13-0.25	0.18	Sanders, In press
Midge (larva), *Chironomus plumosus*	LC	1.0-3.2	1.8	Sanders, In press

* Life cycle or partial life cycle

Geometric mean of chronic values = 0.31 µg/l $\quad \frac{0.31}{5.1} = 0.06$ µg/l

Lowest chronic value = 0.09 µg/l

Table 5. Freshwater residues for toxaphene

Organism	Bioconcentration Factor	Time (days)	Reference
Brook trout (fry), *Salvelinus fontinalis*	76,000	15	Mayer, et al., 1975
Brook trout (yearling), *Salvelinus fontinalis*	16,000	161	Mayer, et al., 1975
Fathead minnow, *Pimephales promelas*	69,000	98	Mayer, et al., 1977
Channel catfish, *Ictalurus punctatus*	26,000	100	Mayer, et al., 1977
Channel catfish (fry), *Ictalurus punctatus*	50,000	30	Mayer, et al., 1977

Maximum Permissible Tissue Concentration

Organism	Action Level or Effect	Concentration (mg/kg)	Reference
Man	edible fish and shellfish	5.0	U.S. FDA Admin. Guideline 7420.09
Domestic animals	animal feed	0.5	U.S. FDA Admin. Guideline 7426.04

Geometric mean fish bioconcentration factor = 44,000

Lowest maximum residue concentration = 0.5 mg/kg

$\frac{0.5}{44,000} = 0.000011$ mg/kg or 0.011 µg/l

Table 6. Other freshwater data for toxaphene

Organism	Test Duration	Effect	Result (ug/l)	Reference
Brook trout, Salvelinus fontinalis	90 days	No effect on growth	<0.039	Mayer, et al. 1975
Brook trout, Salvelinus fontinalis	166 days	Growth inhibition	0.27	Mayer, et al. 1975
Brook trout, Salvelinus fontinalis	11 days	LTC-LC50	4.1	Mayer, et al. 1975
Brook trout, Salvelinus fontinalis	161 days	Decreased reproduction	0.075	Mayer, et al. 1975
Brook trout (fry), Salvelinus fontinalis	60 days	Growth inhibition	0.041	Mayer, et al. 1975
Brook trout (fry), Salvelinus fontinalis	15 days	Mortality	0.041	Mayer, et al. 1975
Fathead minnow, Pimephales promelas	30 days	Growth inhibition	0.097	Mayer, et al. 1977
Fathead minnow (fry), Pimephales promelas	30 days	Growth inhibition	0.054	Mayer, et al. 1977
Fathead minnow, Pimephales promelas	7 days	LTC-LC50	5.3	Mayer, et al. 1977
Channel catfish, Ictalurus punctatus	5 days	LTC-LC50	15.2	Mayer, et al. 1977
Channel catfish, Ictalurus punctatus	30 days	Growth inhibition	0.299	Mayer, et al. 1977
Channel catfish, Ictalurus punctatus	30 days	Backbone quality	0.072	Mayer, et al.. 1977

SALTWATER ORGANISMS

Introduction

Toxaphene has been used as an insecticide for many years; its toxicity, persistence, and bioconcentration potential has been well documented in studies using saltwater plants and animals. Its acute toxicity, particularly to fishes, prompted its use to control populations of undesirable fishes.

Chronic toxicity of toxaphene to saltwater animals has been documented only recently, but its toxicity to plants and bioconcentration by oysters and fishes has been known since the 1960's.

Toxaphene is a mixture of numerous chlorinated terpenes, but which terpenes are most toxic to saltwater biota is unknown because they have not been tested individually.

Acute Toxicity

In flow-through toxicity tests with five fish species (Table 7) unadjusted 48- and 96-hour LC50 values ranged from 0.5 µg/l to 5.5 µg/l (Butler, 1963; 1964; Korn and Earnest, 1974; and Schimmel, et al. 1977). Katz (1961) exposed the threespine stickleback to toxaphene in static tests at 5 and 25°/oo salinity and reported 96-hour LC50 values of 8.6 and 7.8 µg/l, respectively. Freshwater fishes tested were comparably sensitive (Table 1).

The 12 saltwater invertebrate species tested were highly disparate in species sensitivity to toxaphene (Table 8). Crustaceans varied greatly in species sensitivity. Blue crabs were relatively insensitive; the unadjusted 48- and 96-hour LC50 values ranged from 330 µg/l to 2,700 µg/l (Butler, 1963; McKenzie, 1970). Several life stages of the pink shrimp were nearly identi-

cal in sensitivity to toxaphene with the 96-hour LC50 values ranging from 1.4 to 2.2 µg/l (Courtenay and Roberts, 1973; Schimmel, et al. 1977). However, sensitivity of individuals of five early life stages of the drift-line crab exposed to toxaphene in 96-hour toxicity tests was inversely related to the age of the crabs tested. For example, the 96-hour LC50 of stage I larvae was 0.054 µg/l; that for megalopa (the oldest stage tested) was 8.4 µg/l (Table 8). Other than stage I drift-line crab larvae, the most sensitive crustacean tested was the copepod, Acartia tonsa, the 96-hour LC50 being 0.11 µg/l when recalculated by probit analysis (Finney, 1971; Khattat and Farley, 1976). The unadjusted 96-hour LC50 to mactrid clams, the least sensitive species, was 460,000 µg/l (Chaiyarach, et al. 1975). However, the data from toxicity tests such as this with molluscs which can close their valves and avoid direct contact with exposure water for indefinite periods of time may underestimate a chemical's toxicity. In a more appropriate test with molluscs, embryos of Mercenaria mercenaria were also relatively insensitive with a 48-hour EC50 of 1,120 µg/l (Davis and Hidu, 1969).

Chronic Toxicity

Chronic effects of toxaphene on saltwater fishes indicate that concentrations that do not affect individuals in their early stages differ little from 96-hour LC50 values. Goodman, et al. (1978) conducted an embryo-larval study with the sheepshead minnow in which toxaphene was not lethal to embryos at concentrations as high as 2.5 µg/l. Combined embryo and larval mortality during a 28-day exposure to 2.5 µg/l was significantly greater than control mortality, but at 1.1 µg/l mortality was not greater. Therefore,

concentrations not affecting survival or growth of sheepshead minnows in an embryo-larval test were the same as the 96-hour LC50 of toxaphene to juvenile sheepshead minnows. Schimmel, et al. (1977) exposed longnose killifish to toxaphene in a 28-day embryolarval study. Significant effects on survival were evident at 1.3 µg/l, but not at 0.6 µg/l. No 96-hour LC50 data are available for the juvenile of this species; however, it probably would not be greater than 10 times the no-effect concentration in an embryo-larval test (Schimmel, et al. 1977).

The data for saltwater fishes contrast sharply with chronic test data for freshwater fishes (Table 3). The 96-hour LC50 of toxaphene for the channel catfish was nearly 100 times the highest concentration that produced no observable deleterious effects in a chronic study; that for the fathead minnow, Pimephales promelas, was nearly 200 times. Data for four other pesticides support the hypothesis that differences between acute- and chronic-effect concentrations in freshwater and saltwater fishes are similar (Parrish, et al. 1978). Probably either saltwater fishes differ from freshwater fishes in chronic sensitivity to toxaphene because of the innate differences between salt water and fresh water, or the difference in sensitivity may be due to phylogenetic factors, such as those reported by Macek and McAllister (1970). If the latter is true, then a criterion based on a saltwater cyprinodontid fish, such as sheepshead minnow or longnose killifish in an embryo-larval study may not provide adequate protection for other estuarine and marine fishes.

The mysid shrimp is the only saltwater invertebrate species exposed to toxaphene in a lifecycle study (Table 10) (Nimmo,

1977). Exposure to 0.14 µg/l of salt water decreased the number of young produced per female by 82 percent. An unmeasured concentration of 0.067 µg/l did not adversely affect reproduction. The limits on the chronic values (0.07 to 0.12 µg/l) generated using the freshwater cladoceran, Daphnia magna (Table 4), are comparable to those for the saltwater mysid.

Plant Effects

Ukeles (1962) found that five species of algae varied greatly in sensitivity to toxaphene (Table 11). The most sensitive organism was the dinoflagellate, Monochrysis lutheri, its growth being inhibited at a concentration of 0.15 µg/l. Data from Butler (1963) indicated that 1,000 µg/l caused a 90.8 percent decrease in productivity of natural phytoplankton communities.

Residues

The bioconcentration of toxaphene into tissues of saltwater animals has been well studied (Butler, 1960; Goodman, et al. 1978; Lowe, 1964; Lowe, et al. 1970; and Schimmel, et al. 1977) (Table 12). Lowe et al. (1970) exposed eastern oysters, Crassostrea virginica, to a concentration of 0.7 µg/l for 36 weeks, followed by a 12-week depuration period. The maximum bioconcentration factor (BCF), 32,800, was attained after 24 weeks. No toxaphene was found in oyster tissues after the 12-week depuration period.

Goodman, et al. (1978) exposed sheepshead minnow embryos and fry to toxaphene for 28 days and reported an average BCF of 9,800. Schimmel, et al. (1977) exposed newly-hatched and juvenile longnose killifish for 28 days and reported average BCF's of 27,900 and 29,450, respectively.

Therefore, the geometric mean BCF for saltwater fishes (excluding ova of the longnose killifish) was 12,690 and that for oysters exposed to toxaphene was 32,800.

Data Interpretation and Use of Guidelines

The acute toxicity of toxaphene to saltwater organisms may be underestmated when LC50 values are based on unmeasured concentrations, thereby justifying the use of adjustment factors for this test condition. For example, Schimmel, et al. (1977) reported 96-hour LC50 values for five species based on unmeasured and measured concentrations. Four of the five measured values were lower and one was equal to the unmeasured value. Only the test results with measured concentrations are listed in Tables 7 and 8.

Variability in species sensitivity of fishes exposed to toxaphene is approximately a factor of 10 (Table 7) compared with that for invertebrate species tested (approximately a factor of 10^5, not including data on the mactrid clam; Table 8). Therefore, use of the greater species sensitivity factors for invertebrate species appears justified. The use of adjustment factors contained in the Guidelines for species sensitivity produces a Final Fish Acute Value of 0.44 µg/l (Table 7) which is only slightly lower than the lowest adjusted LC50 values. Since the Guidelines provide a Final Fish Acute Value which is lower than or equal to 95 percent of the LC50 values, the sensitivity adjustment factor appears adequate. For invertebrate species, however, the Final Invertebrate Acute Value of 0.12 µg/l (Table 8) is lower than the adjusted LC50 values for nine of eleven (82 percent) species tested. Sesarma cinereum and Acartia tonsa, (Table 8)

would, therefore, not be protected from acute effects of toxaphene at the Final Invertebrate Acute Value. Reasons for providing a less-than-adequate Final Acute Value for the two species above probably lie in the extremely high range (up to 100,000) in LC50 values from species to species. This is significant because these two species are saltwater zooplankters which are especially important as foods and larvae in saltwater systems.

Data from an embryo-larval test (Goodman, et al. 1978) and information from the Guidelines were used to obtain a saltwater fish chronic value for toxaphene (Table 9). No reports of entire life-cycle exposures of saltwater fish were available in the literature, but estimates of chronic values in these tests can be obtained by using procedures in the Guidelines with data on embryo-larval tests. Use of this procedure and a species sensitivity factor in the Guidelines appears to be justified, since the sheepshead minnow has been shown to be generally less sensitive in acute studies than are several other saltwater fishes. No other saltwater fish can now be tested in life-cycle tests for comparison of chronic sensitivity. Therefore, 0.12 µg/l is the Final Fish Chronic Value.

One saltwater invertebrate species, Mysidopsis bahia, has been exposed to toxaphene in a chronic toxicity test (Nimmo, 1977). Using the procedures in the Guidelines, a chronic value of 0.097 µg/l is derived from this test. Using the species sensitivity factor of 5.1, a Final Invertebrate Chronic Value of 0.019 µg/l is derived (Table 10). Since Mysidopsis bahia is a relatively sensitive species, it is believed that this value is adequate to protect 95 percent of invertebrate species exposed chronically to toxaphene.

Data derived from plant studies with toxapene (Table 11) do not generate a Final Plant Value lower than the Final Invertebrate Chronic Value of 0.019 µg/l.

Saltwater residue data for toxaphene (Table 12), based on the average BCF's reported by Goodman, et al. (1978) and Schimmel, et al. (1977) and FDA maximum tissue concentration of toxaphene allowable in animal feed (0.5 mg/kg), produce a Residue Limited Toxicant Concentration (RLTC) of 0.039 µg/l in salt water. Use of the oyster BCF value of 32,800 (Lowe, et al. 1970) and the FDA maximum concentration of toxaphene in edible shellfish (5.0 mg/kg) provides a higher RLTC (0.15 µg/l).

Miscellaneous

No data from Table 13 suggest any more sensitive effects than those already discussed.

CRITERION FORMULATION

Saltwater-Aquatic Life

Summary of Available Data

The concentrations below have been rounded to two significant figures.

Final Fish Acute Value = 0.44 µg/l

Final Invertebrate Acute Value = 0.12 µg/l

Final Acute Value = 0.12 µg/l

Final Fish Chronic Value = 0.12 µg/l

Final Invertebrate Chronic Value = 0.019 µg/l

Final Plant Value = 0.15 µg/l

Residue Limited Toxicant Concentration = 0.039 µg/l

Final Chronic Value = 0.019 µg/l

0.44 x Final Acute Value = 0.053 µg/l

The maximum concentration of toxaphene is the Final Acute Value of 0.12 µg/l and the 24-hour average concentration is the Final Chronic Value of 0.019 µg/l. No important adverse effects on saltwater aquatic organisms have been reported to be caused by concentrations lower than the 24-hour average concentration.

CRITERION: For toxaphene the criterion to protect saltwater aquatic life as derived using the Guidelines is 0.019 µg/l as a 24-hour average and the concentration should not exceed 0.12 µg/l at any time.

Table 7. Marine fish acute values for toxaphene

Organism	Bioassay Method*	Test Conc.**	Time (hrs)	LC50 (ug/l)	Adjusted LC50 (ug/l)	Reference
Sheepshead minnow, Cyprinodon variegatus	FT	M	96	1.1	1.1	Schimmel, et al. 1977
Threespine stickleback, Gasterosteus aculeatus	S	U	96	8.6	4.7	Katz, 1961
Threespine stickleback, Gasterosteus aculeatus	S	U	96	7.8	4.3	Katz, 1961
Striped bass, Morone saxatilis	FT	U	96	4.4	3.4	Korn & Earnest, 1974
Pinfish, Lagodon rhomboides	FT	M	96	0.5	0.5	Schimmel, et al. 1977
Spot, Leiostomus xanthurus	FT	U	48	1.0	0.62	Butler, 1964
White mullet, Mugil curema	FT	U	48	5.5	3.4	Butler, 1963

*S = static, FT = flow-through

**M = measured, U = unmeasured

Geometric mean of adjusted values = 1.61 µg/l $\frac{1.61}{3.7}$ = 0.44 µg/l

Lowest value from a flow-through test with measured concentrations = 0.5 µg/l

Table 8. Marine invertebrate acute values for toxaphene

Organism	Bioassay Method*	Test Conc.**	Time (hrs)	LC50 (ug/l)	Adjusted LC50 (ug/l)	Reference
Eastern oyster, Crassostrea virginica	FT	M	96	16.***	16	Schimmel, et al. 1977
Eastern oyster, Crassostrea virginica	FT	U	96	63.***	48	Butler, 1963
Eastern oyster, Crassostrea virginica	FT	U	96	57.***	44	Butler, 1963
Hard clam (embryo), Mercenaria mercenaria	S	U	48	1,120****	949	Davis & Hidu, 1969
Mactrid clam, Rangia cuneata	S	U	96	460,000****	309,600	Chaiyarach, et al. 1975
Copepod, Acartia tonsa	S	U	96	0.11*****	0.093	Khattat & Farley, 1976
Mysid shrimp (juvenile), Mysidopsis bahia	FT	M	96	6.32	6.32	Nimmo, 1977
Mysid shrimp (adult), Mysidopsis bahia	FT	M	96	3.19	3.19	Nimmo, 1977
Blue crab, Callinectes sapidus	FT	U	48	330.***	109	Butler, 1963
Blue crab, Callinectes sapidus	S	U	96	580	491	McKenzie, 1970
Blue crab, Callinectes sapidus	S	U	96	900	762	McKenzie, 1970
Blue crab, Callinectes sapidus	S	U	96	370	313	McKenzie, 1970
Blue crab, Callinectes sapidus	S	U	96	960	813	McKenzie, 1970
Blue crab, Callinectes sapidus	S	U	96	380	322	McKenzie, 1970
Blue crab, Callinectes sapidus	S	U	96	770	652	McKenzie, 1970

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Table 8. (Continued)

Organism	Bioassay Method*	Test Conc.**	Time (hrs)	LC50 (ug/l)	Adjusted LC50 (ug/l)	References
Blue crab, *Callinectes sapidus*	S	U	96	1,200	1,016	McKenzie, 1970
Blue crab, *Callinectes sapidus*	S	U	96	2,700	2,287	McKenzie, 1970
Blue crab, *Callinectes sapidus*	S	U	96	1,000	847	McKenzie, 1970
Korean shrimp, *Palaemon macrodactylus*	S	U	96	20.3	17.2	Schoettger, 1970
Korean shrimp, *Palaemon macrodactylus*	FT	U	96	20.8	16.0	Schoettger, 1970
Grass shrimp, *Palaemonetes pugio*	FT	M	96	4.4	4.4	Schimmel, et al. 1977
Brown shrimp, *Penaeus aztecus*	FT	U	48	4.9***	1.6	Butler, 1963
Pink shrimp, *Penaeus duorarum*	FT	M	96	1.4	1.4	Schimmel, et al. 1977
Pink shrimp (nauplius), *Penaeus duorarum*	S	U	96	2.2	1.9	Courtenay & Roberts, 1973
Pink shrimp (protozoea), *Penaeus duorarum*	S	U	96	1.8	1.5	Courtenay & Roberts, 1973
Pink shrimp (mysis), *Penaeus duorarum*	S	U	96	1.4	1.2	Courtenay & Roberts, 1973
Mud crab (stage I larva), *Rhithropanoplus harrisii*	S	U	96	43.75	37.1	Courtenay & Roberts, 1973
Drift-line crab (stage I larva), *Sesarma cinereum*	S	U	96	0.054	0.046	Courtenay & Roberts, 1973
Drift-line crab (stage II larva), *Sesarma cinereum*	S	U	96	0.76	0.64	Courtenay & Roberts, 1973

Table 8. (Continued)

Organism	Bioassay Method*	Test Conc.**	Time (hrs)	LC50 (ug/l)	Adjusted LC50 (ug/l)	References
Drift-line crab (stage III larva), Sesarma cinereum	S	U	96	0.74	0.63	Courtenay & Roberts, 1973
Drift-line crab (stage IV larva), Sesarma cinereum	S	U	96	6.8	5.8	Courtenay & Roberts, 1973
Drift-line crab (megalopa), Sesarma cinereum	S	U	96	8.4	7.1	Courtenay & Roberts, 1973

* S = static, FT = flow through

** M = measured, U = unmeasured

*** EC50: Decreased growth of oysters, or loss of equilibrium for brown shrimp or blue crabs.

**** Not used to calculate geometric mean because bivalve egg data and mortality data were not used in calculation of variance. In addition, toxicity can be underestimated when molluscs close their valves and avoid direct exposure.

*****LC50 data recalculated using probit analyses Method of Finney (1971).

Geometric mean of adjusted values = 5.86 µg/l $\frac{5.86}{49}$ = 0.12 µg/l

Lowest value from a flow-through test with measured concentrations = 1.4 µg/l

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Table 9. Marine invertebrate chronic values for toxaphene (Nimmo, 1978)

Organism	Test	Limits (ug/l)	Chronic Value (ug/l)
Mysid shrimp, *Mysidopsis bahia*	LC	0.067-0.14	0.097

Geometric mean of lowest chronic value = 0.097 µg/l. $\frac{0.097}{5.1}$ = 0.019 µg/l

Lowest chronic value = 0.097

Table 10. Marine fish chronic values for toxaphene (Goodman, et al. 1978)

Organism	Test*	Limits (ug/l)	Chronic Value (ug/l)
Sheepshead minnow, *Cyprinodon variegatus*	E-L	1.1-2.5	0.83

* E-L = embryo-larval

Geometric mean of chronic values = 0.83 µg/l $\frac{0.83}{6.7}$ = 0.12 µg/l

Lowest chronic value = 0.83 µg/l

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Table 11. Marine plant effects for toxaphene

Organism	Effect	Concentration (ug/l)	Reference
Alga, *Chlorella* sp.	No growth	70	Ukeles, 1962
Dinoflagellate, *Dunaliella euchlora*	Lethal	150	Ukeles, 1962
Dinoflagellate, *Monochrysis lutheri*	No growth	0.15	Ukeles, 1962
Alga, *Phaeodactylum tricornutum*	Lethal	40	Ukeles, 1962
Alga, *Protococcus* sp.	No growth	150	Ukeles, 1962
Natural phytoplankton communities	90.8% decrease in productivity; ^{14}C	1,000	Butler, 1963

Lowest plant value = 0.15 µg/l

Table 12. Marine residues for toxaphene

Organism	Bioconcentration Factor	Time (days)	Reference
Eastern oyster, *Crassostrea virginica*	32,800	168	Lowe, 1970
Sheepshead minnow, *Cyprinodon variegatus*	9,800	28	Goodman, et al. 1978
Longnose killifish (fry), *Fundulus similis*	27,900	28	Schimmel, et al. 1977
Longnose killifish (juvenile), *Fundulus similis*	29,450	28	Schimmel, et al. 1977
Longnose killifish (adult), *Fundulus similis*	5,400	32	Schimmel, et al. 1977
Longnose killifish (ova of exposed adult), *Fundulus similis*	1,270	14	Schimmel, et al. 1977
Longnose killifish (ova of exposed adult), *Fundulus similis*	3,700	32	Schimmel, et al. 1977

Maximum Permissible Tissue Concentration

Organism	Action Level or Effect	Concentration (mg/kg)	Reference
Man	edible fish and shellfish	5.0	FDA Admin. Guideline 7420.09
Domestic animals	animal feed	0.5	FDA Admin. Guideline 7426.04

Geometric mean shellfish bioconcentration factor = 32,800

Geometric mean fish bioconcentration factor = 12,690

Lowest maximum residue concentration = 0.5 mg/kg

$\frac{0.5}{12,690}$ = 0.000039 mg/kg or 0.039 µg/l

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Table 13. Other marine data for toxaphene

Organism	Test Duration	Effect	Result µg/l	Reference
Eastern oyster, *Crassostrea virginica*	24 hrs	Growth inhibition	100	Butler, 1960
Eastern oyster, *Crassostrea virginica*	4 days	Bioconcentration factor = 11,250		Schimmel, et al., 1977
Grass shrimp, *Palaemonetes pugio*	4 days	Bioconcentration factor = 960		Schimmel, et al. 1977
Pink shrimp, *Penaeus duorarum*	4 days	Bioconcentration factor = 550		Schimmel, et al. 1977
Sheepshead minnow, *Cyprinodon variegatus*	4 days	Bioconcentration factor = 7,620		Schimmel, et al. 1977
Longnose killifish (fry 48 hrs), *Fundulus similis*	28 days	LC50	1.3	Schimmel, et al. 1977
Longnose killifish (juvenile), *Fundulus similis*	28 days	LC50	0.9	Schimmel, et al. 1977
Longnose killifish (adult), *Fundulus similis*	14 days	95% mortality	1.7	Schimmel, et al. 1977
Spot, *Leiostomus xanthurus*	144 hrs	50% mortality	0.5	Lowe, 1964

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Mammalian Toxicology and Human Health Effects

EXPOSURE

Ingestion from Water

Several routine monitoring studies of United States surface waters conducted prior to 1975 did not detect toxaphene (Brown and Nishioka, 1967; Lichtenberg, et al. 1970; Manigold and Schulze, 1969; Mattraw, 1975; Schafer, et al. 1969; Schulze, et al. 1973; Weaver, et al. 1965). Lichtenberg (1971) and Schulze, et al. (1973) placed the toxaphene lower detection limit at 0.5 to 1.0 µg/l, whereas other organochlorides can be detected at concentrations about two orders of magnitude lower. Nicholson, et al. (1964, 1966) detected toxaphene in drinking water obtained from Flint Creek, Ala. from 1959 to 1965. Mean concentrations of 0.05 to 0.10 µg/l were noted during the first four years when toxaphene usage in the area was high, but dropped to 0.01 to 0.05 µg/l in the last three years. A survey of commercial drinking water samples conducted by the U.S. Environmental Protection Agency (1976a) during 1975 and 1976 found no detectable levels of toxaphene in 58 samples; the limit of detection was 0.05 µg/l.

Toxaphene has been detected in water around areas where it was applied to crops as an insecticide. In California, Johnston, et al. (1967) detected toxaphene residues in 60 of 61 analyses of surface effluents in Panoche Drain Water (average 2.009 µg/l and range of 0.100 to 7.900 µg/l) and in 13 of 66 analyses of San Joaquin Valley tile drainage effluents (average 0.528 µg/l and range of 0.130 to 0.950

µg/l). Also, in California, Bailey and Hannum (1967) monitored toxaphene in 17 of 26 surface water samples (average concentration 0.23 µg/l). The San Joaquin District, California Department of Water Resources (1963-1969) detected toxaphene in 51 of 422 (12 percent) tile drainage effluents (0.02 to 0.5 µg/l); in 216 of 447 (48 percent) of surface drains in Central Valley (0.04 to 71.00 µg/l); in 88 of 712 (12 percent) of Central Valley surface waters (0.02 to 0.93 µg/l); and in 8 of 200 (4 percent) of California bays and surface waters.

In Alabama, the Flint Creek watershed was monitored during the years 1959 to 1965 (Cohen, et al. 1961; Grzenda and Nicholson, 1965; Grzenda, et al. 1964; Nicholson, 1969; Nicholson, et al. 1964; 1966). This water-shed drains an agricultural district where the major pesticide source is from small cotton farms, major users of toxaphene (Nicholson, et al. 1964). During this study, toxaphene was detected (carbon absorption followed by chloroform extraction) in paired samples of raw Flint Creek water and treated drinking water obtained from Flint Creek. Toxaphene concentrations ranged from the limits of detection to 0.410 µg/l, with a mean of approximately 0.07 µg/l. Since the recovery was approximately 50 percent (i.e., 48 percent for the 1 ng/l spiked samples and 42 percent for the 0.5 ng/l samples), actual residues may have averaged about 0.14 µg/l. The toxaphene concentrations in treated and untreated water samples were not significantly different, indicating that treatment of drinking water does not reduce toxaphene concentrations.

Although Mattraw (1975) did not detect toxaphene in surface water in an organochlorine residue survey in Florida, toxaphene was found in 3.2 percent of the sediment samples (claimed lower detection limit of 0.05 µg/l). Barthel, et al. (1969) also found detectable toxaphene residues in sediments at 11 sites on the lower Mississippi River. Herring and Cotton (1970) detected toxaphene in 11 of 20 Mississippi Delta Lakes at a maximum concentration of 1.92 µg/l. Sediments from 10 of these lakes had a maximum toxaphene concentration of 2.46 µg/l.

Toxaphene contamination also has been documented in an area surrounding a toxaphene manufacturing plant. The University of Georgia Marine Institute (Reimold, 1974; Reimold and Durant, 1972a, b, 1974; Durant and Reimold, 1972) has monitored toxaphene contamination in surface waters, sediment, and biota of waters receiving the effluent of the Hercules, Inc. plant located on Terry Creek, Brunswick, Ga, the largest producer of toxaphene in the United States. The average monthly toxaphene concentration in the plant's effluent has decreased from a high of 2332 µg/l in August 1970 to a low of 6.4 µg/l in June 1974. Dye experiments have shown that the effluent is diluted by a factor of 10 after it reaches Terry Creek (Reimold, 1974). The Institute (Reimold and Durant, 1972a, b; Durant and Reimold, 1972) analyzed sediment at three locations downstream of the plant outfall. Samples were collected prior to a dredging operation in June 1971 at three sites downstream: 0.2 miles from the outfall at a location 50 yards from its intersection

with another creek; 0.8 miles from the plant outfall; and 1.4 miles from the plant outfall and 50 yards from the end of Terry Creek (junction with Back River). Reimold and Durant (1972b) measured 32.56 µg/l as the average toxaphene concentration in sediment cores within Terry Creek Marsh. The highest residue concentration measured in the surrounding water was 15 µg/l before dredging.

Ingestion from Food

Estimates of toxaphene exposure from dietary intake can be made from the U.S. Food and Drug Administration (FDA) market basket survey, the FDA survey of unprocessed food and feed samples, and the U.S. Department of Agriculture (USDA) survey of meat and poultry. In the FDA market basket survey, food samples are prepared for consumption (i.e., cooked, or otherwise processed) prior to monitoring for pesticide residues (Duggan and McFarland, 1967). The market basket items are grouped by commodity class (e.g., dairy products, leafy vegetables, legume vegetables) and are intended to represent a 2-week diet for a 16- to 19-year-old male (Duggan and Corneluissen, 1972). The results of these surveys, from their inception to the most recently published report, are summarized in Table 1. From 1964 to 1972, food samples were obtained from five cities: Boston, Mass., Baltimore, Md., Los Angeles, Calif., Kansas City, Mo., and Minneapolis, Minn. Of the 26 positive samples encountered during this period, 19 were in Los Angeles, four were in Baltimore, and one was in Boston. Based on the estimates of daily intake made by Duggan and Corneluissen (1972),

TABLE 1
Toxaphene Residues Found in Food and Drug Administration Market Basket Survey, 1964 to 1975.

Monitoring Period	No. of Composits	No. of Composits Positive	% Occurrence	Commodities Contaminated (No. of Composits of Each Commodity Contaminated	Range of Levels (mg/kg)	Daily Intake	Reference
June 1964-April 1965	216	0	0.0	--	--	0	Duggan, et al. 1966
June 1965-April 1966	312	3	1.0	Leafy vegetables(1) and garden fruits(2)	0.048-0.38	0.002	Duggan, et al. 1967
June 1966-April 1967	360	0	0.0	--	--	0	Martin and Duggan, 1968
June 1967-April 1968	360	4	1.1	Meat, fish, or poultry(1) leafy vegetables(1), garden fruits(2)	0.064-0.375	0.002	Corneliussen, 1969
June 1968-April 1969	360	13	3.6	Garden fruits(6), meat, fish, or poultry(1), legume vegetables(2), root vegetables(1), leafy vegetables(3)	0.022-0.33	0.004	Corneliussen, 1970
June 1969-April 1970	360	4	1.1	Leafy vegetables(2), garden fruits(2)	0.080-0.132	0.001	Corneliussen, 1972
June 1970-April 1971	360	1	0.3	Root vegetables(1)	trace		Manske and Corneliussen, 1974
June 1971-July 1972	420	1	0.2	Leafy vegetables(1)	0.1		Manske and Johnson, 1975
Aug. 1972-July 1973	360	0(1)[b]	0.0	--	(0.005)[b]		Johnson and Manske, 1975
Aug. 1973-July 1974	360	3	0.8	Garden fruits(3)	trace-0.163		Manske and Johnson, 1976
Aug. 1974-July 1975	240	1	0.4	Leafy vegetables(1)	0.118		Johnson and Manske, 1977

[a]From Duggan and Corneliussen, 1972.
[b]Strobane.

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and assuming an average body weight of 70 kg, the estimated daily dose of dietary toxaphene over the period of June 1964 to April 1970 was 0.021 µg toxaphene/kg body weight/day. This estimate is based on food samples from a limited number of cities, most of which are not located in areas of high toxaphene usage. The more recent (1972 to 1975) results of the market basket survey suggest that the current daily dietary dose may be substantially lower; however, it is equally possible that the dietary doses for individuals located in the Mississippi Delta (an area of high toxaphene usage) could be substantially higher. The U.S. EPA (1977) recently compiled the results of the FDA survey on unprocessed food and feed samples. As indicated in Table 2, the percent of occurence of toxaphene contamination suggests significant potential exposures to field workers.

TABLE 2
Toxaphene Residues Found in Food and Drug Administration Survey of Unprocessed Food and Feed Samples, 1972 to 1976[a]

Year	# of commodities contaminated	# of samples checked	# of positive samples	% of occurrence	Commodity most frequently contaminated
1972	10	3516	118	3.3	Leaf & Stem Vegetables
1973	15	2906	150	4.8	Leaf & Stem Vegetables
1974	8	1919	109	4.6	Fish
1975	12	2317	118	5.0	Fish
1976	15	4228	257	6.0	Fish

[a]U.S. EPA, 1977.

The only published information encountered in the USDA survey of meat and poultry is contained in the World Health Organization (WHO) (1974a) monograph on toxaphene. This information is summarized in Table 3.

TABLE 3
Residues of Toxaphene in Meat and Poultry Products[a]

Species	No. of tissues analyzed		No. with a residue		No. with toxaphene	
	1969	1970 (6 mos)	1969	1970 (6 mos)	1969	1970
Meat						
Cattle	739	583	712	NA[b]	2	0
Calves	142	67	141	NA	0	0
Swine	1964	1076	1741	NA	0	2
Sheep	312	137	303	NA	0	1
Goats	12	8	10	NA	0	0
TOTAL	3169	1871	2907	1721	2	3
Poultry						
Young chickens	1909	1405	1898	NA	2	0
Mature chickens	78	-	77	NA	0	0
Turkeys	169	67	164	NA	0	0
Ducks	42	8	41	NA	0	0
Geese	1	2	1	NA	0	0
Other	-	4	-	NA	0	0
TOTAL	2199	1486	2181	1472	2	0

[a]World Health Organization, 1974a.
[b]Breakdown by species not available from 1970 interim report.

Similar but unpublished information covering the years 1973 to 1978 has been obtained from the U.S. Department of Agriculture (1978) and is summarized in Table 4. These data indicate that toxaphene is found consistently from year to year in the fat of cattle, although the incidence of contamination is extremely low. During this survey period, only six samples were in excess of the tolerance limit (7.0 ppm; see Existing Guidelines and Standards section). Of

TABLE 4
Residues of Toxaphene in Fat Samples of Meat and Poultry Products at Slaughter in the United States[a]

Animal	Number of Positive Samples/Total Number of Samples (%)											
	1973		1974		1975		1976		1977		1978[b]	
Cattle	9/710	(1.27)	2/1117	(0.18)	3/1733	(0.17)	3/1785	(0.17)	4/880	(0.45)	1/432	(0.23)
Calves	1/84	(1.19)	0/284	(0.0)	0/269	(0.0)	0/327	(0.0)	0/124	(0.0)	0/62	(0.0)
Sheep & Goats	2/289	(0.69)[c]	1/371	(0.27)	0/356	(0.0)	0/250	(0.0)	0/100	(0.0)	0/36	(0.0)
Swine	4/232	(1.72)	2/329	(0.61)	0/324	(0.0)	1/442	(0.23)	0/215	(0.0)	0/179	(0.0)
Chicken	3/530	(0.57)	1/1138	(0.09)	0/777	(0.0)	0/927	(0.0)	1/375	(0.27)	0/191	(0.0)
Turkeys	3/517	(0.58)	0/735	(0.0)	0/554	(0.0)	0/456	(0.0)	0/303	(0.0)	0/64	(0.0)
Ducks & Geese	0/95	(0.0)	0/148	(0.0)	0/246	(0.0)	0/267	(0.0)	0/186	(0.0)	0/39	(0.0)
Rabbits	0/19	(0.0)			0/11	(0.0)	0/65	(0.0)	0/21	(0.0)	0/14	(0.0)
Horses	0/44	(0.0)	3/266	(1.13)	0/261	(0.0)	0/217	(0.0)	0/112	(0.0)	0/20	(0.0)
TOTAL	22/2520	(0.87)	9/4388	(0.21)	3/3971	(0.08)	4/4736	(0.08)	5/3216	(0.22)	1/1037	(0.10)

[a] U.S. Department of Agriculture, 1978.
[b] first two quarters only
[c] listed as lamb

these six violations, five were in fat samples from cattle, one of which occurred in the first quarter of 1978. The data summarized in Tables 3 and 4 indicate that toxaphene is not a widespread contaminant in meat and poultry products.

As detailed in the Ecological Effects section of this criterion document, toxaphene in water can be bioconcentrated in fish by factors of 50,000 and more, based on laboratory studies and measurements of whole body residues. However, in assessing potential human dietary exposure, the primary concern is with residues bioconcentrated in the edible portion or fillet. Working with adult brook trout, Mayer, et al. (1975) found that toxaphene was bioconcentrated in the fillet by a factor of 8,000 when fish were kept in water containing toxaphene at 0.5 µg/l for 161 days. At a nominal concentration of 0.041 µg/l - which is still greater than the concentrations of toxaphene found in drinking water (see Ingestion from Water section) - the bioconcentration factor for the fillet was less than 2,400. Toxaphene residues found in fish from toxaphene-treated lakes are generally consistent with levels obtained during laboratory studies and indicate that fish bioconcentrate toxaphene by a factor of several thousand. For example, Terriere, et al. (1966) found that total mean body residues in rainbow trout in lakewater were several µg/g compared to approximatley 0.5 µg/l in water (bioconcentration factor of 9,000 to 19,000), which is comparable to the bioconcentration observed experimentally by Mayer, et al. (1975) with total body residues in brook trout.

A bioconcentration factor (BCF) relates the concentration of a chemical in water to the concentration in aquatic organisms, but BCF's are not available for the edible portions of all four major groups of aquatic organisms consumed in the United States. Since data indicate that the BCF for lipid-soluble compounds is proportional to percent lipids, BCF's can be adjusted to edible portions using data on percent lipids and the amounts of various species consumed by Americans. A recent survey on fish and shellfish consumption in the United States (Cordle, et al. 1978) found that the per capita comsumption is 18.7 g/day. From the data on the 19 major species identified in the survey and data on the fat content of the edible portion of these species (Sidwell, et al. 1974), the relative consumption of the four major groups and the weighted average percent lipids for each group can be calculated:

Group	Consumption (Percent)	Weighted Average Percent Lipids
Freshwater fishes	12	4.8
Saltwater fishes	61	2.3
Saltwater molluscs	9	1.2
Saltwater decapods	18	1.2

Using the percentages for consumption and lipids for each of these groups, the weighted average percent lipids is 2.3 for consumed fish and shellfish.

The above approach have been used to estimate a bioconcentration factor for toxaphene. Measured steady-state bioconcentration factors were obtained for toxaphene using five species:

Organisms	BCF	Percent Lipids	Adjusted BCF	Reference
Eastern oyster, *Crassostrea virginica*	32,800	1.5	50,293	Lowe, 1970
Sheepshead minnow, *Cyprinodon variegatus*	9,800	5	4,508	Goodman, et al. 1978
Brook trout (fry), *Salvelinus fontinalis*	76,000	4.5	38,844	Mayer, et al. 1975
Brook trout, (yearling), *Salvelinus fontinalis*	16,000	4.5	8,178	Mayer, et al. 1975
Fathead minnow, *Pimephales promelas*	69,000	8	19,838	Mayer, et al. 1977
Channel catfish, *Ictalurus punctatus*	26,000	3.2	18,688	Mayer, et al. 1977
Channel catfish (fry), *Ictalurus punctatus*	50,000	3.2	35,938	Mayer, et al. 1977

Each of these measured BCF's was adjusted from the percent lipids of the test species to the 2.3 percent lipids that is the weighted average for consumed fish and shellfish. The geometric mean was obtained for each species, and then for all species. Thus, the weighted average bioconcentration factor for toxaphene and the edible portion of all aquatic organisms consumed by Americans is calculated to be 18,000.

Inhalation

The highest toxaphene residues in air have been found in areas where toxaphene is applied for agricultural purposes (especially cotton production) (Arthur, et al. 1976; Miss. Agric. Exp. Sta., 1976; Stanley, et al. 1971; Tabor, 1965 and 1966). Studies in cotton-growing areas demonstrate that airborne residues are highest during the cotton growing season and decrease to low levels after harvesting, but spring tilling releases soil residues to the air. The recent identification of ng/m^3 levels over the Atlantic Ocean, where toxaphene has not been applied, establishes that toxaphene residues move with air currents analagous to DDT (Bidleman, et al. 1976; Bidleman and Olney, 1975).

Arthur, et al. (1976) reported a 3-year (January 1972 to December 1974) study of toxaphene air residues at Stoneville, Miss., which is located in the southern cotton belt. Over this period, toxaphene concentrations were highest in August (1540.0, 268.8, and 903.6 ng/m^3) and lowest in January (0.0, 0.0, 10.9 ng/m^3). The mean monthly concentration was 167 ng/m^3. In a more recent unpublished survey of the Mississippi area, conducted from January 1976 to July 1976, the mean measured toxaphene concentration in air was 18.7 ng/m^3, with the highest concentration found during June and July (42.09 ng/m^3) (Miss. Agric. Exp. Sta., 1976). Earlier studies (Tabor, 1965, 1966) conducted in seven southern agricultural communities, detected toxaphene at only two sites: Leland, Miss. where toxaphene levels

ranging from 1.2 to 7.5 ng/m^3 were found in 6 of 15 samples from July to September 1963; and Newellton, Tex., where toxaphene levels ranging from 3.1 to 15 ng/m^3 were found in 6 of 10 samples. Both of these communities were cotton-growing areas.

Comparative geographic studies of toxaphene air concentrations suggest that toxaphene contamination is most pervasive in southern states. From 1967 to 1968 Stanley, et al. (1971) attempted to monitor toxaphene at nine locations: Baltimore, Md., Buffalo, N.Y., Dothan, Ala., Fresno, Calif., Iowa City, Iowa, Orlando, Fla., Riverside, Calif., Salt Lake City, Utah, and Stoneville, Miss. Toxaphene was found in only three locations, all in the southern part of the country: Dothan (11 of 90 samples at 27.3 to 79.0 ng/m^3), Orlando (9 of 79 samples at 20.0 to 2520 ng/m^3), and Stoneville (57 of 98 samples at 16.0 to 111.0 ng/m^3). Similarly, Bidleman, et al. (1976) monitored toxaphene at five sites in North America. As indicated in Table 5, the more southern sites evidenced considerably higher concentrations of toxaphene.

TABLE 5
Toxaphene Residues in Air Samples at Five North American Sites[a]
(Bidleman, et al. 1976)

Location and Date	Number of Samples	Range (ng/m^3)
Kingston, Rhode Island, 1975	6	0.04 - 0.4
Sapelo Island, Georgia, 1975	6	1.7 - 5.2
Organ Pipe Cactus National Park, Arizona, 1974	6	2.7 - 7.0
Hays, Kansas, 1974	3	0.083 - 2.6
Northwest Territories, Canada, 1974	3	0.04 - 0.13

[a]Bidleman, et al. 1976.

Toxaphene has also been monitored in the atmosphere over the east coast of the U.S., near Bermuda, and over the open ocean (Bidleman and Olney, 1975). With respect to the above discussion of geographic distribution, it is not too surprising that a sample taken at Sapelo Island, Ga. is substantially greater (mean of 2.8 ng/m^3) than the samples taken at Bermuda (mean of 0.79 ng/m^3) or over the open ocean (mean of 0.53 ng/m^3), since substantial amounts of toxaphene are used in the south on cotton.

These monitoring studies clearly suggest that toxaphene is a prevalent atmospheric contaminant in areas where this pesticide is used, particularly in the southern United States. Taking the mean monthly toxaphene concentration of 167 ng/m^3 noted by Arthur, et al. (1976) over a 3-year period in Stoneville, Miss., and assuming (1) that the average human weighs 70 kg and breathes 24 m^3 of air per day, and (2) that all

of the toxaphene breathed into the lungs is absorbed,[1] the average daily dose of toxaphene from air is approximately 0.057 μg/kg.[2] This is approximately twice the estimated daily intake of toxaphene from the diet (see Ingestion from Food section) based on the FDA 1964 to 1970 market basket survey. An average national level of toxaphene exposure from air cannot be estimated from the available data. However, taking the average concentration monitored by Bidleman and Olney (1975) over the open ocean (0.53 ng/m^3), the daily intake of toxaphene from air would be 0.18 ng/kg.

Dermal

No direct information is available on the importance of dermal absorption in total human exposure to toxaphene. Data from toxicity studies with laboratory mammals (see Acute, Subacute, and Chronic Toxicity section) indicate that toxaphene can be absorbed across the skin in toxic amounts by humans. However, incidences of dermal absorption of toxaphene by humans are restricted to occupational or accidental exposures to large amounts of toxaphene. For those exposed to only background levels of toxaphene, dermal absorption is not likely to be a significant route of entry.

[1]Assuming 100 percent absorption is common EPA policy, but in this case is very conservative since human studies of occupationally exposed individuals suggest no absorption (see Absorption section).

[2]It should be noted that 0.057 μg/kg is a maximum or worst case value due to (1) assumption of 100 percent absorption and (2) use of a mean monthly toxaphene concentration from a high toxaphene use area.

PHARMACOKINETICS

Absorption

The recently completed U.S. EPA (1978) study suggests that inhalation exposures to toxaphene do not result in sufficient absorption by humans to cause quantifiable levels in the blood. The study found no detectable levels of toxaphene in the blood of 54 workers occupationally exposed to toxaphene. However, of 53 personal air samples analyzed, 30 had quantifiable levels of toxaphene and 19 had trace levels. In the same study, one individual not occupationally exposed to toxaphene was found to have elevated toxaphene blood levels associated with the consumption of toxaphene-contaminated fish (see Excretion section), indicating significant absorption after oral exposure.

Inferences on the absorption of toxaphene by laboratory mammals can be made from some of the available toxicity data. Absorption across the alimentary tract, skin, and respiratory tract is indicated by the adverse effects elicited by toxaphene on oral, dermal, and inhalation exposures. Based on toxicity studies detailed in the Acute, Subacute, and Chronic Toxicity section, the vehicle used in the administration of toxaphene has a marked influence on lethality. This effect is probably attributable to differences in the extent and/or rate of absorption. In oral exposures, toxaphene has a much lower LD50 when administered in a readily absorbed vehicle - e.g. corn oil or peanut oil - than when given in an indigestible vehicle such as kerosene. Similarly, dermal applications of toxaphene in solution with mineral

oil, dimethyl phthalate, or water are much more toxic than similar applications of toxaphene in powder preparations (Lackey, 1949 a, b; Conley, 1952). Documented cases of human poisoning by toxaphene indicate that man may absorb toxic levels following oral, dermal, or inhalation exposures (McGee, et al. 1952; Pollock, 1958; Warraki, 1963). When administered or applied in comparable lipophilic solvents, the ratio of oral LD50 to dermal LD50 is about 0.1 (Tables 6 and 8). This suggests that toxaphene is absorbed more completely and/or more rapidly from the alimentary tract than from the skin. The pronounced variability in time to death after toxaphene ingestion indicates marked individual differences in the rate of toxaphene absorption and/or differences in susceptibility to toxaphene intoxication.

Distribution

Toxaphene is readily distributed throughout the body, with highest residues found in fat tissue. Three hours after single intubations of Cl-36 labelled toxaphene in peanut oil: acacia, rats had detectable levels of Cl-36 activity in all tissues examined (kidney, muscle, fat, testes, brain, blood, liver, intestines, esophagus, spleen, and stomach) with the highest levels being found in the stomach and blood. By nine days after dosing, 6.57 percent of the administered dose (measured as Cl-36 activity) remained in the organism, with most of the activity found in the fat, blood, liver, and intestines (Crowder and Dindal, 1974). In a similar single dose study using rats with corn oil as the vehicle (Ohsawa, et al. 1975), both C-14 labelled

toxaphene (8.5 mg/kg) and C-14 labelled 2,2,5-endo, 6-exo, 8,9,10-heptachloroborane (2.6 mg/kg) (a component of toxaphene) were found primarily in the fat, liver, kidneys, and blood after 14 and 9 days, respectively. These patterns are consistent with toxaphene redistribution from the fat via the circulatory system to kidneys and liver prior to urinary and fecal elimination (see Metabolism and Excretion sections).

The predominance of fat storage has also been demonstrated in 12-week feeding studies with rats (Clapp, et al. 1971) and 2-year feeding studies with rats and dogs (Lehman, 1952a; Hercules, Inc., undated). In all these studies, toxaphene residues were highest in fat tissue but remained below the levels administered in the diet. This suggests that toxaphene is not likely to be biomagnified in terrestrial organisms, and is consistent with the relatively rapid elimination of toxaphene by mammals (see Excretion section).

Metabolism

Toxaphene undergoes reductive dechlorination, dehydrochlorination, and hydroxylation in mammalian systems.

In the study by Crowder and Dindal (1974) using Cl-36 labelled toxaphene, about 68 percent of the activity was recovered as ionic chloride. Similarly, Ohsawa, et al. (1975) found that of seven Cl-36 labelled toxaphene fractions administered by intubation to rats, all were dechlorinated by about 50 percent. Based on the recovery of both C-14 and Cl-36 labelled toxaphene, these investi-

gators concluded that only three percent of the original dose is excreted unchanged and only two percent is eliminated as carbon dioxide.

For technical (i.e., commercial grade) toxaphene, both reductive dechlorination and dehydrochlorination occur in reduced bovine blood hematin solutions, and 50 percent dechlorination has been noted in toxaphene incubated with rat liver microsomes and reduced nicotinamide adenine dinucleotide phosphate (NADPH) under anaerobic conditions (Khalifa, et al. 1976). Reductive dechlorination has also been demonstrated for heptachloroborane, a component of toxaphene, (Saleh, et al. 1977; Chandurkar, 1977; Pollock, 1978).

Toxaphene has been shown to yield a type I binding spectra with hepatic cytochrome P-450 of rats, mice, and rabbits which suggests that toxaphene may serve as a substrate for the hepatic microsomal mixed-function oxidase system (Kulkarni, et al. 1975). Type II binding has not been observed. Metabolism by the hepatic microsomal mixed function oxidase system is further suggested by the potentiation of toxaphene by piperonyl butoxide (Saleh, et al. 1977) and the demonstrated NADPH dependance for the <u>in vitro</u> hydroxylation of nonachloroborane (a toxaphene component) by rat liver microsomes (Chandurkar, 1977).

In comparing the chromatographic patterns of toxaphene residues found in the liver, feces, and fats, both Pollock (1978) and Saleh, et al. (1977) have noted that only fat residues approximate those of whole toxaphene, while residues in both the liver and feces are consistently more polar.

Excretion

The half-life of C-14 or Cl-36 labelled toxaphene in rats after single oral doses appears to be from one to three days, with most of the elimination occurring via the urine and feces (Crowder and Dindal, 1974; Ohsawa, et al. 1975). Only a small portion of the urine and fecal metabolites are eliminated as glucuronide or sulfate conjugates (Chandurkar, 1977).

As mentioned in the Absorption section, elevated toxaphene blood levels in one individual in the U.S. EPA (1978) study were associated with the consumption of toxaphene-contaminated fish (catfish fillet with a toxaphene residue of 52 µg/g wet weight). On the first day that blood samples were taken, toxaphene was found in the blood of this individual at a concentration of 142 ppb. Eleven days after this measurement, the concentration of toxaphene in the blood had fallen to 47 ppb. By 14 days after the initial measurement, toxaphene blood levels were below the limit of detection (30 ppb).

EFFECTS

Acute, Sub-acute, and Chronic Toxicity

Information on the acute oral toxicity of toxaphene to laboratory animals is summarized in Table 6. In cases of acute intoxication, toxaphene, like most chlorinated hydrocarbon insecticides, appears to act as a central nervous system stimulant. However, unlike DDT, toxaphene does not significantly affect conduction in the rat superior cervical ganglion (Whitcomb and Santolucito, et al. 1976). Published reports of human cases of acute toxaphene poisoning

TABLE 6
Acute Oral Toxicity of Technical Toxaphene to Laboratory Mammals

Organism	Vehicle	LD50 (mg/kg)	Reference
Rats			
Unspecified strain	Unspecified	69	Lehman, 1951
Wistar, male, 3-4 weeks, 50-60 g, fasted	Cottonseed oil	220 ± 33[a]	Boyd and Taylor, 1971
Sherman, male, 90 days, 175 g, fasted	Peanut oil	90(67-122)[b]	Gaines, 1960
Sherman, female, 90 days, 175 g, fasted	Peanut oil	80(70-91)[b]	Gaines, 1960
	Peanut oil	40	Shelanski and Gellhorn, undated
	Peanut oil	90	Hercules Inc., undated
	Corn oil	120-125	Shelanski and Gellhorn, undated
	Corn oil	60	Hercules Inc., undated
Mice	Corn oil	112	Hercules Inc., undated
	Unspecified oil	80	Rico, 1961
Cats	Peanut oil	25-40	Hercules Inc., undated
	Unspecified oil	100	Rico, 1961
Dogs	Peanut oil	~25	Lackey, 1949a
	Corn oil	49	Hercules Inc., undated
	Unspecified oil	100	Rico, 1961
Rabbits	Peanut oil	75-100	Hercules Inc., undated
Guinea Pigs	Corn oil	270	Hercules Inc., undated
	Unspecified oil	80	Rico, 1961

[a] ± standard error.
[b] 95 percent confidence interval.

by ingestion are summarized in Table 7. In these cases, convulsions are the most consistent clinical signs of intoxication. Similar effects have been observed in both rats and dogs (Lehman, 1951). Along with convulsions, hyperreflexia has been noted in dogs (Lackey, 1949a, b), rats (Boyd and Taylor, 1971), and humans (Haun and Cueto, 1967). Additional unpublished reports (U.S. EPA, 1976e) of poisoning in humans describe the major symptoms of oral intoxication as vomiting, convulsions, cyanosis, and coma. Based on a review of the acute toxicity of toxaphene to experimental mammals and cases of human poisoning, Conley (1952) has estimated the minimum lethal oral dose of toxaphene for man to be between 30 and 103 mg/kg body weight. In rats, pathological effects of toxaphene include cloudy swelling and congestion of the kidneys, fatty degeneration and necrosis of the liver, and decreased spermatogenesis (Boyd and Taylor, 1971). Mehendale (1978) has reported that toxaphene (100 mg/kg in the diet for eight days) inhibits hepatobiliary function in rats.

The acute dermal toxicity of toxaphene is summarized in Table 8. Toxaphene appears to be somewhat less toxic when administered dermally. In rats the ratios of dermal to oral LD50's range from 10 to 12 (Gaines, 1960; 1969; Hercules Inc., undated). Without providing documentation, Hayes (1963) estimates the hazardous dermal dose for humans at 46 grams. For a 70 kg man, this is approximately 660 mg/kg. Dermal LD50's for rats range from 780 to 1075 mg/kg (Gaines, 1960; 1969; Hercules Inc., undated).

TABLE 7
Case Studies of Toxaphene Poisoning in Humans in which Ingestion is the Primary Route of Entry

Case No.	1[a]	2[a]	3[a]	4[a]	5[a]	6[a]	7[b]
Subject(s)	Male 2 yr 8 mo	Male, 4 yrs	Male, 1 yr 5 mo	Male, 2 yrs	Female, 20 yrs Female, 16 yrs Female, 12 yrs	Male, adult Male, young Female, adult	Female, 9 mo
Nature of toxaphene	Wax	Emulsion in water	60% in solvents	20% in solution	Residue of spray in food	Residue of spray in food	Powder, 13.8% toxaphene, 7.04% DDT
Dose	Unknown	Unknown	~100 mg/kg	Unknown	9.5-47 mg/kg	Unknown	Unknown
Time to react to onset of symptoms	~7 hours	2 hours	N.S.	N.S.	1.5-4 hours	4 hours	A few hours
Symptoms	Convulsions	Convulsions 2-5 minute intervals	Convulsions intermittent	Convulsions, intermittent; mild cerebral excitement; aimless jerking motion and excessive muscular tensions of extremities, marked pharyngeal and laryngeal spasms; labored respiration; cyanosis	Nausea; vomiting; convulsions	No nausea; spontaneous vomiting; convulsions jerking and transitory movements; muscular rigidity; periods of unconsciousness; amnesia(?)	Vomiting; diarrhea; convulsions; hyperreflexia; tachycardia; b.p.140/100; labored respiration; respiratory failure
Outcome	Death	Death	Death	Recovery	Recovery	Recovery	Death
Time to death or recovery	9.5 hours	6 hours	11 hours	12 hours	~12 hours	<1 day(?)	~9 hours

[a] McGee, et al. 1952
[b] Haun and Cueto, 1967

TABLE 8
Acute Dermal Toxicity of Toxaphene to Laboratory Mammals

Organism	Vehicle	Dose (mg/kg)	Response	Reference
Rats Sherman, male, >90 days, > 175 g, unfasted	Xylene	1075 (717-1613)	LD50 (95% Confidence Interval)	Gaines, 1960 and 1969
Rats Sherman, female, >90 days, > 175 g, unfasted	Xylene	780 (600-1014)	LD50 (95% Confidence Interval)	Gaines, 1960 and 1969
Rats	Xylene	930	LD50	Hercules Inc., undated
Rabbits	Dust	>4000	LD50	Hercules Inc., undated
Rabbits	Peanut oil	< 250	LD50	Hercules Inc., undated

Table 9 summarizes the effects of subacute oral administration of toxaphene to laboratory mammals. Except for convulsions observed in dogs given 5 mg/kg/day, none of the exposures detailed in Table 9 resulted in clinical signs of toxaphene poisoning. The ability of dogs to tolerate large cumulative doses (176 to 424 mg/kg) when given at 4 mg/kg/day suggests a rather sharp threshold level for central nervous system stimulation. This is consistent with information discussed in the Excretion section, showing that toxaphene is eliminated relatively rapidly. A similar pattern is seen in rats on intraperitoneal injection. Ohsawa and coworkers (1975) have found that male rats injected with 50 mg toxaphene (approximately 300 mg/kg) every 48 hours tolerated cumulative doses of 700 to 2,000 mg/kg (over 10 times the single oral LD50 dose) before marked lethality occurred.

In subacute exposures, which do not cause apparent central nervous system stimulation, no increases in mortality are noted. However, pathological changes of the kidneys and liver, as well as changes in blood chemistry, seem to be common features of subclinical toxaphene intoxication.

Ortega, et al. (1951) (using rats) and Lackey (1949a) (using dogs) have noted similar changes in liver histology. Morphologically, these changes appear as vacuoles of plasma with occasional red blood cells found within hepatic cells. This condition, referred to as hydropic accumulation, is distinct from fatty degeneration. In neither rats nor dogs was hydropic accumulation associated with the destruction

TABLE 9
Subacute Oral Toxicity of Toxaphene

Organism	Vehicle	Duration	Dose mg/kg/day or ppm in diet)	Estimated cumulative dose (mg/kg)	Response[a]	Reference
Mice, both albino and wild strains	Diet	Several weeks or months	50 mg/kg/day (250-480 ppm)	300	Changes in blood chemistry and urine protein	Baeumler, 1975
Rats	Diet	12 weeks	189 ppm		No apparent adverse effects	Clapp, et al. 1971
Rats	N.S.[b]	7 months	1.2-4.8 mg/kg/day	250-1000	Temporary change in blood chemistry	Grebenyuk, 1970
Rats, Sherman, male and female, 100 g	Diet	2-9 months	50 and 200 ppm		Questionable liver pathology	Ortega, et al. 1957
Rats and guinea pigs	Diet	6 months	100-800 ppm		No significant effect	Shelanski and Gellhorn, undated
Dogs	Corn oil	"A few days"	5 mg/kg/day	~15-35	Convulsion	Lackey, 1949a
	Corn oil	44 days	4 mg/kg/day	176	Questionable liver pathology: renal tubular degeneration	Lackey, 1949a
	Corn oil	106 days	4 mg/kg/day	424	Questionable liver pathology: renal tubular degeneration	Lackey, 1949a

[a] See text for details.
[b] N.S. - not specified.

of hepatic cells. However, Ortega, et al. (1957) also noted occasional masses of red blood cells invading the cytoplasm of liver cells in areas of hypertrophy and margination. In addition to liver damage, Lackey (1949a) also noted widespread degeneration of the tubular epithelium, occasionally accompanied by inflammation of the pelvis of the kidney. Identical pathological changes were seen in dogs surviving prolonged dermal exposures to toxaphene (Lackey, 1949b).

As noted in Table 9, alterations in clinical chemistry have also been seen in subacute oral toxaphene exposures. Mice with no clinical signs of intoxication evidenced consistent increases in serum acid phosphatase, glutamicpyruvic transaminase, and gamma-glutyamyl transpeptidase activities, along with increased neutrophil counts and changes in urine protein (Baeumler, 1975). At a much lower daily dose, rats had only a transient increase in serum alkaline phosphatase during the 5th month of intoxication and showed no variation in urine hippuric acid (Grebenyuk, 1970). Increases in all of the above enzyme activities are consistent with the mild liver pathology associated with subacute toxaphene exposure.

Lehman (1952b) states that the 90-day dermal LD50 of toxaphene (as a dry wax) is 40 mg/kg in rabbits. No details of symptoms or pathology are provided.

Hercules Inc. (undated) has conducted experimental dermal and inhalation exposures of human volunteers to toxaphene. Toxaphene doses of 300 mg/day applied to the skin of 50 volunteers for 30 days produced no observable toxic

effects. Similarily, cotton patches treated with toxaphene produced neither sensitization nor primary skin irritation when applied to the skin of 200 subjects. Shelanski (1974) indicates that humans exposed to toxaphene mists of 500 mg/m^3 of air for 30 minutes daily for ten consecutive days followed by three daily exposures three weeks later showed no adverse effects, based on physical examinations as well as blood and urine tests.

However, Warraki (1963) has attributed two cases of acute bronchitis with miliary lung shadows to inhalation of toxaphene during applications of toxaphene formulation spray. Warraki does not specify the carriers used during the toxaphene spray applications of the cases that he summarized. However, he did indicate that toxaphene is usually applied as an emulsifiable concentrate containing 60 percent toxaphene, 35 percent kerosene, 3 percent xylol, and 2 percent emulsifier. Both individuals, male adults, had been exposed to toxaphene sprays from 1-1/2 to 2 months before the onset of pulmonary insufficiency. Maximum breathing capacity was between 19 and 22 percent of normal. Both adverse affects observed (pulmonary insufficiency and lung lesions) were reversible within 3 months after toxaphene exposure was discontinued. No central nervous system effects were noted. One case of allergic rhinitis in a worker exposed to toxaphene by inhalation has been reported. However, details on the duration of exposures were not given (U.S. EPA, 1976e).

Long-term exposures to low dietary levels of toxaphene are summarized in Table 10. All studies note some form of liver pathology in rats at dietary levels of 100 mg/kg or above. At 100 mg/kg, cytoplasmic vacuolization similar to that seen on subacute oral exposure was noted by Kennedy, et al. (1973). Lehman (1952) noted both cytoplasmic vacuolization and fatty degeneration of the liver in rats fed 100 mg/kg. At 25 mg/kg diet, Fitzhugh and Nelson (1951) did observe increased liver weight with minimal liver cell enlargement. Unpublished studies on rats, dogs, and monkeys by Hercules Inc. (undated) are in general agreement with the above published reports. The lowest dietary level of toxaphene producing unequivocal liver damage over a two-year feeding period is 20 mg/kg diet. Only at relatively high concentrations -i.e., 1,000 mg/kg diet - does chronic toxaphene exposure elicit central nervous system effects characteristic of acute intoxication.

No cases of chronic human intoxication have been encountered in the literature.

Synergism and Antagonism

Induction of hepatic microsomal mixed-function oxidase appears to account for most of the interactions of toxaphene with other compounds. In rats pretreated with aldrin or dieldrin and evidencing increased liver O-dealkylase and O-demethylase activities, toxaphene 96-hour LD50 values were approximately two times higher (indicating decreased toxicity) than those of rats given no pretreatment. Similarly, pretreatment with DDT, a known inducer of hepatic microsomal

TABLE 10
Chronic Toxicity of Toxaphene at
Low Dietary Levels to Laboratory Mammals

Organism	Duration of feeding	Toxaphene concentration in diet	Response[a]	Reference
Rats, Sprague Dawley	3 generations	25 mg/kg	No effect	Kennedy, et al. 1973[b]
		100 mg/kg	Liver pathology	
Rats	Lifetime	25 mg/kg	No effect	Lehman, 1952[a]
		100 mg/kg	Liver pathology	
Rats	Lifetime	25 mg/kg	Liver pathology	Fitzhugh and Nelson, 1951
Rats	2 years	25 mg/kg	No effect	Hercules Inc. undated
	2 years	100 mg/kg	Slight liver damage	
		1000-1600 mg/kg	CNS stimulation	
Dogs	2 years	5-20 mg/kg	No effect	Hercules Inc. undated
Dogs	2 years	40 mg/kg	Slight liver degeneration	
		200 mg/kg	Moderate liver degeneration	
Dogs	1360 days (3.7 years)	5mg/kg/day[a]	Liver necrosis	Hercules Inc. undated
Monkeys	2 years	10-15 mg/kg (0.64-0.78 mg/kg/day)	No clinical or histological effects	Hercules Inc. undated

[a]Administered in capsules containing toxaphene dose in corn oil; 5 mg/kg/day equivalent to 200 mg/kg in diet.
[b]Diets prepared fresh weekly. (The other studies in this table did not specify frequency).

mixed-function oxidase, resulted in a threefold increase in the 96-hour LD50 of toxaphene in rats (Deichmann and Keplinger, 1970). Piperonyl butoxide, which inhibits the metabolism of many toxicants by mixed-function oxidase, has been shown to potentiate the toxicity of toxaphene in house flies (Saleh, et al. 1977).

When administered by intubation to rats, equitoxic combinations of toxaphene with parathion, diazinon, or trithion were less toxic than would be expected based on the assumption of simple similar action (Keplinger and Deichmann, 1967).

Cases of acute human intoxication by toxaphene-lindane mixtures have been reported. In one instance, (Pollock, 1958) a 70-year-old male had his hands in contact with a toxaphene-lindane solution for two hours. After ten hours, the following symptoms developed: headache, poor coordination, lassitude, severe nausea, and vomiting. Over the next week, this individual exhibited mild hyperthermia, flaccid musculature, and decreased response to stimuli. Only after nine days did the individual become semicomatose. At no time were convulsions or hyperreflexia noted. These signs and symptoms are not characteristic of toxaphene or lindane poisoning (Matsumura, 1975) and differ markedly from the previously described cases of acute oral toxaphene poisoning in humans. While clinical signs of intoxication may be expected to show some variation with different routes of entry, such profound variation is uncommon with the chlorinated insecticides. Gaines (1960, 1969) noted no difference

between signs of intoxication in rats orally and dermally exposed to a variety of pesticides. Lackey (1949 a, b) similarly notes no remarkable differences in the response of dogs to subacute oral and dermal doses of toxaphene.

Two cases of acute plastic anemia associated with dermal exposure to toxaphene/lindane mixtures have been reported (U.S. EPA, 1976e). One of these cases resulted in death due to acute myelomonocytic leukemia which was presumed to be secondary to the development of plastic anemia. Thus, while toxic anemia has not been reported in laboratory mammals in acute toxaphene poisoning, such an effect may be hazardous in man in instances also involving lindane exposure.

Teratogenicity

In a study by Kennedy, et al. (1973), male and female rats were fed dietary levels of 25 mg/kg diet and 100 mg/kg toxaphene. Gross and microscopic pathology of F3 weanlings revealed no indication of teratogenic effects. Further, no statistically signficiant variations from controls were noted in either dose group for any of the following parameters: mating index, fertility index, pregnancy index, parturition index, mean viable litter size, live birth index, five-day survival index, lactation index, or weaning body weights of offspring. One of 16 females from each dose group resorbed an entire litter. This was not seen in any of the 32 control females but did occur in tests with another pesticide, delnav.

In multigeneration studies of mice given toxaphene at 25 mg/kg diet, no effects on fertility, gestation, viability, lactation, or survival indices were observed (Keplinger, et al. 1970).

In addition to these long-term dietary studies, one study (Chernoff and Carver, 1976) has been conducted in which toxaphene in corn oil was administered to pregnant female rats and mice from days 7 to 16 of gestation at doses of 15, 25, and 35 mg/kg/day. All doses produced signs of maternal and fetal toxicity but no teratogenic effects.

DiPasquale (1977) has examined the effects of toxaphene on fetal guinea pig development. In this study, toxaphene was administered to pregnant females at a dose of 15 mg/kg body weight orally from day 21 to day 35 of gestation. No effects were noted on anatomical development of the fetus. The only sign of fetotoxicity was a decrease in collagen-containing structures. This was attributed to a functional deficiency of vitamin C related to mixed-function oxidase induction. Maternal guinea pigs showed a slight loss of body weight but no effects were seen on maternal liver weight or mortality.

Mutagenicity

Epstein, et al. (1972) have used a modified dominant lethal assay in mice to evaluate the mutagenic potential of a variety of chemical agents including toxaphene. In this study, four groups of male ICR/Ha Swiss mice were given toxaphene intraperitoneally - single doses of 36 mg/kg and 180 mg/kg - and orally - five doses of 8 mg/kg/dose and

16 mg/kg/dose. After dosing, the treated males were mated to groups of untreated females over an eight-week period. Based on measurements of early fetal deaths per pregnancy and the percent of females with early fetal deaths, the toxaphene-treated groups did not differ significantly from controls. Thus, in this strain of mice, toxaphene apparently does not produce chromosomal abnormalities that preclude zygote development.

Hill (1977) has summarized information on the mutagenicity testing of toxaphene in bacterial systems. Ames tests have been conducted on Salmonella typhimurium strains TA-1535, TA-1537, TA-1538, TA-98, and TA-100 with and without metabolic activation by non-induced mammalian liver fractions. Positive results were obtained for strains TA-98 (frameshift mutation) and TA-100 (base pair substitution) only in tests without metabolic activation. All other tests were negative. A "high temperature" toxaphene has elicited positive dose response increases in strains TA-98 and TA-100 only with metabolic activation. All the above tests were conducted by Litton Bionetics Inc. for Hercules, Inc.

In addition to these studies, work has been conducted on the mutagenicity of toxaphene in the Salmonella system by Dr. Kim Hooper of Bruce Ames' group in Berkeley, Calif. (Hill, 1977). His results indicate that toxaphene and toxaphene subfractions are mutagenic to strain TA-100 with and without activation by Aroclor-induced rat microsomes. Mutagenic activity was decreased in those tests using microsomal activation.

A recently completed study by U.S. EPA (1978) found no significant differences in the rates of chromosomal aberrations in leukocytes between groups of individuals occupationally exposed to toxaphene and groups with no occupational exposures to toxaphene.

Carcinogenicity

Under contract to the Natl. Cancer Inst., Gulf South Research Institute has recently completed a carcinogenicity bioassay of toxaphene (Natl. Cancer Inst. 1979). It should be noted that this study, which was conducted from 1971 to 1973, did not follow current NCI protocols (Natl. Cancer Inst. 1977). Specifically, only ten animals were used in each matched control group, and matched-fed control groups were not utilized. In this study, groups of Osborne-Mendel rats and B6C3F1 hybrid mice were exposed to technical-grade toxaphene in the diet for 80 weeks. Details of the dose schedule and number of animals used are provided in Tables 11 and 12.

Toxaphene was added to the feed in acetone. In addition, 2 percent corn oil was added to the diet as a dust suppressant. Actual dietary toxaphene concentrations, which were confirmed by gas-liquid chromotography, did not deviate from the nominal concentration by more than 6.9 percent. In addition to the matched control groups indicated in these tables, pooled control groups were used in the statistical analyses. For rats, pooled controls consisted of matched controls from similar bioassays on captan, chloraben, lindane, malathion, and picloram, as well as the matched con-

TABLE 11
Toxaphene Chronic Feeding Studies in Rats[a]

Sex and Test Group	Initial No. of Animals(b)	Toxaphene in Diet(c) (mg/kg	Time on Study Dosed(d) (weeks)	Time on Study Observed(e) (weeks)	Time-Weighted Average Dose(f) (mg/kg)
Male					
Matched-Control	10	0		108-109	
Low-Dose	50	1,280	2		556
		640	53		
		320	25		
		0		28	
High-Dose	50	2,560	2		1,112
		1,280	53		
		640	25		
		0		28	
Female					
Matched-Control	10	0		108-109	
Low-Dose	50	640	55		540
		320	25		
		0		30	
High-Dose	50	1,280	55		1,080
		640	25		
		0		30	

[a] National Cancer Institute, 1979.
[b] All animals were 5 weeks of age when placed on study.
[c] Initial doses shown were toxic; therefore, doses were lowered after 2 weeks and again at 53 or 55 weeks, as shown.
[d] All animals were started on study on the same day.
[e] When diets containing toxaphene were discontinued, dosed rats and their matched controls were fed control diets without corn oil for 20 weeks, then control diets (2 percent corn oil added) for an additional 8 weeks.
[f] Time-weighted average dose $= \frac{\Sigma(\text{dose in ppm} \times \text{no. of weeks at that dose})}{\Sigma(\text{no. of weeks receiving each dose})}$

TABLE 12
Toxaphene Chronic Feeding Studies in Mice[a]

Sex and Test Group	Initial No. of Animals[b]	Toxaphene in Diet[c] (mg/kg)	Time on Study: Dosed[d] (weeks)	Time on Study: Observed[e] (weeks)	Time-Weighted Average Dose[f] (mg/kg)
Male					
Matched-Control	10	0		90-91	
Low-Dose	50	160	19		99
		80	61		
		0		11	
High-Dose	50	320	19		198
		160	61		
		0		10	
Female					
Matched-Control	10	0		90-91	
Low-Dose	50	160	19		99
		80	61		
		0		11	
high-Dose	50	320	19		198
		160	61		
		0		10	

[a] National Cancer Institute, 1979.
[b] All animals were 5 weeks of age when placed on study.
[c] Initial doses shown were toxic; therefore, doses were lowered at 19 weeks, as shown.
[d] All animals were started on study on the same day.
[e] When diets containing toxaphene were discontinued, dosed mice and their matched controls were fed control diets without corn oil for 7 weeks, then control diets (2 percent corn oil added) for an additional 3 to 4 weeks.
[f] Time-weighted average dose = $\frac{\Sigma(\text{dose in ppm} \times \text{no. of weeks at that dose})}{\Sigma(\text{no. of weeks receiving each dose})}$

trols from the toxaphene bioassay. For mice, pooled controls consisted of matched controls from similar bioassays on lindane, malathion, phosphamidon, and tetrachlorvinphos, as well as the matched controls from the toxaphene study. Organisms used in all pooled control groups were of the same strains, from the same suppliers, and examined by the same pathologists.

During the course of this study, both rats and mice evidenced signs of general toxic effects. Both male and female rats in the high-dose group developed body tremors at week 53. From week 52 to week 80, other clinical signs, which occurred primarily in toxaphene-dosed rats, included diarrhea, dyspnea, pale mucous membranes, alopecia, rough hair coats, dermatitis, ataxia, leg paralysis, epistaxis, hematuria, abdominal distention, and vaginal bleeding. Female rats in both dose groups had lower mean body weights than the matched controls. No dose-related effect on mortality was noted in any of the rat test groups. In mice, males and females in each dose group displayed a significant increase in mortality when compared to the matched controls. In high-dose male mice, mean body weights were generally lower than those in the matched control group. Clinical signs of toxicity in mice included abdominal distention, diarrhea, alopecia, rough hair coats, and dyspnea.

The effects of dietary toxaphene on tumor incidence in male rats, female rats, male mice, and female mice are summarized in Tables 13, 14, 15, and 16, respectively.

TABLE 13
Analyses of the Incidence of Primary Tumors in Male Rats
Fed Toxaphene in the Diet (a,b)

Topography: Morphology	Matched Control	Pooled Control	Low Dose	High Dose
Liver: Neoplastic Nodule(c)	1/9 (11)	1/52 (2)	6/44 (14)	4/45 (9)
P Values(d)	N.S.	N.S.	P = 0.034**	N.S.
Weeks to First Observed Tumor	109	--	108	94
Pituitary: Chromophobe Adenoma, Carcinoma, NOS, or Adenoma, NOS(c)	3/7 (43)	8/46 (17)	13/42 (31)	5/31 (16)
P Values(d)	N.S.	N.S.	N.S.	N.S.
Weeks to First Observed Tumor	102	--	85	95
Adrenal: Adenoma, NOS, Cortical Adenoma, or Carcinoma	4/9 (44)	5/52 (10)	5/41 (12)	3/37 (8)
P Values(d,e)	P = 0.019 (N)	N.S.	P - 0.043 (N)*	P - 0.020 (N)*
Weeks to First Observed Tumor			85	85
Spleen: Hemangioma(c)	0/9 (0)	0/49 (0)	3/45 (7)	3/42 (7)
P Values(d)	N.S.	N.S.	N.S.	N.S.
Weeks to First Observed Tumor	--	--	83	85
Thyroid: Follicular-cell Carcinoma or Adenoma(c)	1/7 (14)	2/44 (5)	7/41 (17)	9/35 (26)
P Values(d)	N.S.	P - 0.007	N.S.	P - 0.008**
Weeks to First Observed Tumor	109	--	104	56

[a]A National Cancer Institute, 1979.
[b]Dosed groups received time-weighted average doses of 556 or 1,112 ppm.
[c]Number of tumor-bearing animals/number of animals examined at site (percent).
[d]Beneath the incidence of tumors in a control group is the probability level for the Cochran-Armitage test when P less than 0.05; otherwise, not significant (N.S.) is indicated. Beneath the incidence of tumors in a dosed group is the probability level for the Fisher exact test for the comparisons of that dosed group with the matched-control group (*) or with the pooled-control group (**) when P less than 0.05 for either control group; otherwise, not significant (N.S.) is indicated.
[e]A negative trend (N) indicates a lower incidence in a dosed group than in a control group.

TABLE 14
Analyses of the Incidence of Primary Tumors in Female Rats
Fed Toxaphene in the Diet(a,b)

Topography: Morphology	Matched Control	Pooled Control	Low Dose	High Dose
Integumentary System: Malignant Fibrous Histiocytoma of the Subcutaneous Tissue(c)	0/10 (0)	0/55 (0)	1/50 (2)	3/49 (6)
P Values(d)	N.S.	N.S.	N.S.	N.S.
Weeks to First Observed Tumor	--		105	83
Mammary Gland: Fibroadenoma(c)	1/10 (10)	6/55 (11)	10/50 (20)	10/49 (20)
P Values(d)	N.S.	N.S.	N.S.	N.S.
Weeks to First Observed Tumor	87	--	19	67
Liver: Hepatocellular Carcinoma or Neoplastic Nodule(c)	1/10 (10)	1/55 (2)	5/42 (12)	4/40 (10)
P Values(d)	N.S.	N.S.	N.S.	N.S.
Weeks to First Observed Tumor	109	--	108	109
Pituitary: Chromophobe Adenoma, Carcinoma, or Adenoma, NOS(c)	3/8 (38)	17/51 (33)	15/41 (37)	23/39 (59)
P Values(d)	P = 0.046	P = 0.012	N.S.	P = 0.013**
Weeks to First Observed Tumor	85	--	75	79
Thyroid: Follicular-celle Adenoma(c)	0/6 (0)	1/46 (2)	1/43 (2)	7/42 (17)
P Values(d)	P = 0.022	P = 0.008	N.S.	P = 0.021**
Weeks to First Observed Tumor	--	--	102	105

TABLE 14
Analyses of the Incidence of Primary Tumors in Female Rats
Fed Toxaphene in the Diet(a,b)

Topography: Morphology	Matched Control	Pooled Control	Low Dose	High Dose
Adrenal: Cortical Adenoma or Carcinoma(c)	0/8 (0)	3/50 (6)	3/44 (7)	6/43 (14)
P Values(d)	N.S.	N.S.	N.S.	N.S.
Weeks to First Observed Tumor	--	--	104	87
Uterus: Endometrial Stromal Polyp(b)	0/9 (0)	5/53 (9)	9/41 (22)	5/45 (11)
P Values(c)	N.S.	N.S.	N.S.	N.S.
Weeks to First Observed Tumor	--	--	87	109

[a]National Cancer Institute, 1979.
[b]Dosed groups received time-weighted average doses of 540 or 1,080 mg/kg.
[c]Number of tumor-bearing animals/number of animals examined at site (percent).
[d]Beaneath the incidence of tumors in a control group is the probability level for the Cochran-Armitage test when P less than 0.05; otherwise not significant (N.S.) is indicated. Beneath the incidence of tumors in a dosed group is the probability level for the Fisher exact test for the comparison of that dosed group with the matched-control group (*) or with the pooled-control group (**) when P less than 0.05 for either control group; otherwise, not significant (N.S.) is indicated.

TABLE 15
Anaylses of the Incidence of Primary Tumors in Male Mice
Fed Toxaphene in the Diet(a,b)

Topography: Morphology	Matched Control	Pooled Control	Low Dose	High Dose
Liver: Hepatocellular Carcinoma(c)	0/10 (0)	4/48 (8)	34/49 (69)	45/46 (98)
P Values(d)	P less than 0.001	P less than 0.001	P less than 0.001*	P less than 0.001*
			P less than 0.001**	P less than 0.001**
Weeks to First Observed Tumor	--	--	73	59
Liver: Hepatocellular Carcinoma or Neoplastic Nodule(c)	2/10 (20)	7/48 (15)	40/49 (82)	45/46 (98)
P Values(d)	P less than 0.001	P less than 0.001	P less than 0.001*	P less than 0.001*
			P less than 0.001**	P less than 0.001**
Weeks to First Observed Tumor	90	--	73	59

[a] A National Cancer Institute, 1979.
[b] Dosed groups received time-weighted average doses of 99 or 198 mg/kg.
[c] Number of tumor-bearing animals/number of animals examined at site (percent).
[d] Beaneath the incidence of tumors in a control group is the probability level for the Cochran-Armitage test when P less than 0.05; otherwise not signficant (N.S.) is indicated. Beneath the incidence of tumors in a dosed group is the probability level for the Fisher exact test for the comparison of that dosed group with the matched-control group (*) or with the pooled-control group (**) when P less than 0.05 for either control group; otherwise, not significant (N.S.) is indicated.

TABLE 16
Analyses of the Incidence of Primary Tumors in Female Mice
Fed Toxaphene in the Diet (a,b)

Topography: Morphology	Matched Control	Pooled Control	Low Dose	High Dose
Liver: Hepatocellular Carcinoma(c)	0/9 (0)	0/48 (0)	5/49 (10)	34/49 (69)
P Values(d)	P less than 0.001	P less than 0.001	P = 0.030**	P less than 0.001*
				P less than 0.001**
Weeks to First Observed Tumor	--	--	89	72
Liver: Hepatocellular Carcinoma or Neoplastic Nodule(c)	0/9 (0)	0/48 (0)	18/49 (37)	40/49 (82)
P Values (d)	P less than 0.001	P less than 0.001	P = 0.026*	P less than 0.001*
			P less than 0.001**	P less than 0.001**
Weeks to First Observed Tumor	--	--	89	72

[a] National Cancer Institute, 1979.
[b] Dosed groups received time-weighted average doses of 99 or 198 mg/kg.
[c] Number of tumor-bearing animals/number of animals examined at site (percent).
[d] Beneath the incidence of tumors in a control group is the probability level for the Cochran-Armitage test when P less than 0.05; otherwise not significant (N.S.) is indicated. Beneath the incidence of tumors in a dosed group is the probability level for the Fisher exact test for the comparison of that dosed group with the matched-control group (*) or with the pooled-control group (**) when P less than 0.05 for either control group; otherwise, not significant (N.S.) is indicated.

In male rats in the high dose group, a significant increase was noted in the incidence of follicular-cell carcinomas or adenomas of the thyroid. Of the nine thyroid tumors which were found in this group, two were carcinomas. A significant increase of follicular-cell adenomas of the thyroid was also noted in the high-dose group of female rats. No carcinomas of the thyroid were found in this group. In both of these groups, the development of thyroid tumors was dose-related. A significant increase was also noted in the incidence of chromophobes, adenomas, chromophobe carcinomas, and adenomas of the pituitary in the high-dose group female rats. However, an examination of historical control data on the incidence of pituitary tumors in female rats suggested that an association between the administration of toxaphene and the development of pituitary tumors could not be maintained based on the results of this study.

In both male and female mice, significant increases were noted in the incidence hepatocellular carcinomas and in the incidence of hepatocellular carcinomas combined with neoplastic nodules of the liver.

Based on the results of this study, the National Cancer Institute has concluded that "Toxaphene was carcinogenic in male and female B6C3F1 mice, causing increased incidences of hepatocellular carcinomas. The test results also suggest carcinogenicity of toxaphene for the thyroid of male and female Osborne-Mendel rats" (Natl. Cancer Inst. 1979).

Litton Bionetics, Inc. (1978) reported a study in the B6C3F1 strain of male and female mice fed at doses of 7, 20, and 50 ppm toxaphene in the diet which showed a statistically significant excess of hepatocellular tumors (hepatocellular adenoma plus hepatocellular carcinoma) in male mice, but only at the 50 ppm dose.

Strobane, a chlorinated terpene pesticide related to toxaphene, has been shown to cause an increase in liver tumor in male but not female mice (Innes, et al. 1969).

CRITERION FORMULATION

Existing Guidelines and Standards

Standards for toxaphene in air, water, and food have been established or recommended by groups within the United States, international agencies, and agencies of other governments. All these standards were set before the results of the National Cancer Institute bioassay of toxaphene for carcinogenicity were available.

Both the Occupational Safety and Health Administration (39 FR 23540) and the American Conference of Governmental Industrial Hygienists (1977a) have established a time-weighted average value of 500 $\mu g/m^3$ for toxaphene in the air of the working environment. The American Conference of Governmental Industrial Hygienists (1977b) based this standard on unpublished acute and chronic toxicity studies conducted in the 1950's and on comparisons of the toxicity of toxaphene with DDT and Lindane. A tentative short-term exposure limit for toxaphene has been set at 1.0 mg/m^3 (Am. Conf. Gov. Ind. Hyg., 1977a).

The national interim primary drinking water standard for toxaphene is 5 µg/l (40 FR 11990; U.S. EPA 1976b, 1976c). This standard is based on the reported organoleptic effects of toxaphene at concentrations above 5 µg/l (Cohen, et al. 1961; Sigworth, 1965). A standard of 25 µg/l was also calculated based on a concentration of 10 mg/kg in the diet, which was estimated to give an average daily dose of 1 mg/kg body weight, as the lowest long-term level with minimal or no effects in rats (Lehman, 1965). This standard was calculated using the following assumptions:

weight of rat = 300 g
daily food consumption of rat = 50 g
weight of average human adult = 70 kg
average daily water intake for man = 2 liters
safety factor - 1/500
dietary intake = trace (assume zero)

From these assumptions, the maximum safe daily dose for human was estimated to be 3.4 µg/kg body weight (U.S. EPA, 1976b). It should be noted, however, that the assumption of 50 g daily food consumption for a 300 g rat is probably excessively high.

Based on a study by Fitzhugh and Nelson (1951) summarized in Table 10, in which rats evidenced increased liver weight and hepatic cell enlargement after exposure to toxaphene at 25 mg/kg diet for two years, the acceptable daily intake for man has been estimated at 1.25 µg/kg (Natl. Acad. Sci., 1977). This is based on (1) the estimate that the daily dose in rats during the Fitzhugh and Nelson study was equivalent to 1.25 mg/kg body weight and (2) the application of a safety factor of 1,000. Assuming a human body weight of 70 kg and a daily water consumption of 2 liters, the suggested no-adverse effect level from water was set at 8.75 µg/l (assigning 20 percent of the total ADI to water) or 0.44 µg/l (assigning 1 percent of the total ADI to water) (Natl. Acad. Sci., 1977).

Effluent standards for toxaphene manufacturers have been set at 1.5 µg/l for existing facilities and 0.1 µg/l for new facilities (U.S. EPA, 1976d).

Tolerances established by the U.S. Food and Drug Administration for toxaphene residues in various agricultural products are as follows:

Residue level (mg/kg)	Product	Reference
7	Fat of meat from cattle, goats, and sheep	22 FR 4615
	Fat of meat from hogs	24 FR 4727
	Fat of meat from horses	27 FR 7492
	Cranberries, hazelnuts, hickory nuts, horseradish, parsnips, pecans, peppers, pimentos, rutabagas, walnuts	22 FR 4615
	Collards, kale, spinach	27 FR 7492
6	Crude soybean oil	31 FR 12435
5	Barley, oats, rice, rye, and wheat	23 FR 477
	Sorghum grain	25 FR 5335
	Cottonseed	26 FR 11799
3	Pineapple and bananas[a]	27 FR 4913
2	Soybeans, dry form	31 FR 9453
0.1	Sunflower seeds	U.S. EPA, 1977

[a]of which not more than 0.3 mg/kg shall be in pulp after the peel is removed and discarded.

In Canada, the tolerance for toxaphene in citrus fruits is 7.0 mg/kg. In both the Netherlands and West Germany, the corresponding standard is 0.4 mg/kg (Gunther, 1969).

The World Health Organization has not yet established an acceptable daily intake level for toxaphene (WHO, 1974a, 1974b, 1976). The following information is considered necessary by WHO (1974b) before an acceptable daily intake can be established:

1. Adequate toxicological information on camphechlor (toxaphene) as currently marketed, including a carcinogenicity study.

2. Comparative studies evaluating the toxicological hazard associated with polychlorinated camphene of different manufacture used in worldwide agriculture.

3. Before recommendations can be made concerning residues from the use of camphechlor, other than that conforming to FAO specifications, information is needed on the composition, uses, and residues arising from such products.

The following guideline levels for toxaphene in the specified foods have been recommended (WHO, 1974a):

Fat of meat of cattle, sheep, goats, and pigs	5 mg/kg
Broccoli, brussels sprouts, cabbage, celery, collards, eggplant, kale, kohlrabi, lettuce, okra, peppers, pimentos, spinach, tomatoes, barley, rice (rough), rye, sorghum, bananas (whole), pineapple, beans (snap, dry, lima), peas, cauliflower, oats, wheat, shelled nuts, carrots, onions, parsnips, radishes, rutabagas	2 mg/kg
Soybeans, peanuts (ground-nut), cotton-seed oil (refined), rape-seed oil (refined), soybean oil (refined), peanut oil (refined), maize, rice (finished)	0.5 mg/kg
Milk and milk products (fat basis)	0.5 mg/kg

These recommendations are based on levels which might be expected if good application practices are followed and do not reflect a judgement concerning potential human hazard.

The International Joint Commission of the United States and Canada (1977) has recommended a water standard of 0.008 µg/l for the protection of aquatic life. This standard is based on the study by Mayer, et al. (1975) which found that toxaphene at 0.039 µg/l caused a significant increase in mortality and a significant decrease in growth in brook

trout fry over a 90-day period. The standard of 0.008 µg/l is obtained by applying a safety factor of 0.2.

Current Levels of Exposure

Quantitative estimates of human exposure to toxaphene are extremely difficult to make based on the data presented in the Exposure section. The three major obstacles are:

1. The wide variation in toxaphene concentrations noted in food, water, and air.
2. Conflicting information concerning the trend of toxaphene residues in food.
3. The marked seasonal and geographic difference in toxaphene concentrations found in air and food.

Given these problems, a conservative approach in estimating exposure to toxaphene is necessary.

The best available estimate of dietary intake is 0.021 µg/kg/day, based on the U.S. Food and Drug Administration market basket surveys between 1964 and 1970 (Duggan and Corneliussen, 1972). Although more recent market basket surveys indicate a decrease in the incidence of toxaphene contamination (Table 1) and the U.S. Department of Agriculture survey suggests that the incidence of toxaphene contamination of raw meat has remained relatively stable since 1969 (Tables 2 and 3), the U.S. Food and Drug Administration survey of unprocessed food samples shows an almost two-fold increase in the incidence of toxaphene contamination between 1972 and 1976 (Table 2). Given this conflicting information, the current dietary intake is estimated to be 0.042 µg/kg/day, twice that noted by Duggan and Corneliussen (1972).

No satisfactory estimate can be made of average national inhalation exposures. In areas where toxaphene is not used, inhalation exposure may be negligible. Even in areas of high use, the apparent low absorption of toxaphene across the lungs suggests that inhalation may not be a significant source of exposure.

These admittedly tenuous exposure estimates are summarized as follows:

Source	Estimate Intake
Water	no estimate
Food	0.042 ug/kg/day
Air	0

Special Groups at Risk

Individuals working with toxaphene or living in areas where toxaphene is used or produced would seem to be at higher risk than the general population. However, as indicated previously (see Mutagenicity section), an increased incidence of chromosomal aberration has not been noted in groups with occupational exposure to toxaphene (U.S. EPA, 1978). Further, of 32 samples of human adipose tissue obtained from autopsy or surgery cases in areas of high toxaphene usage, only one sample contained detectable levels of toxaphene (0.13 ppm). This sample was from an individual who lived in the Mississippi Delta, an area of high toxaphene use, and who therefore potentially was exposed to toxaphene through agricultural use (U.S. EPA, 1978). Thus, there is no firm data to support the assumption that individuals living in high use areas or individuals with occupational exposure to toxaphene are at greater risk than the general population.

Basis and Derivation of Criterion

Various water concentrations have already been recommended for toxaphene (see Existing Guidelines and Standards section in the Criterion Document). These concentrations, with the rationale, are summarized below:

Standard	Rationale	Source
5.0 µg/l	Organoleptic effects	U.S. EPA, 1976b
8.75 µg/l	Non-carcinogenic mammalian toxicity	Natl. Acad. Sci., 1977
0.44 µg/l	Non-carcinogenic mammalian toxicity	Natl. Acad. Sci., 1977
0.008 µg/l	Aquatic toxicity data	Int. Joint Comm., 1977

Estimated risk levels for toxaphene in water can be calculated using the linear, non-threshold model described in Federal Register FR 15296, 1979. The results of the National Cancer Institute bioassay of toxaphene for carcinogenicity is presented in Appendix I. This model assumes a risk of 1 in 100,000 of developing cancer as a result of drinking 2 liters of water per day containing toxaphene at the concentrations used in the bioassay. Allowances are also made for consuming fish from toxaphene-contaminated waters. The results of these calculations are summarized in Table 17. Taking the results of these calculations from the lowest dose shown to cause a significant increase in tumor incidence, a toxaphene criterion of 0.467 ng/l can be calculated.

TABLE 17

Concentrations of Toxaphene in Water Estimated to Induce No More than One Excess Cancer per 100,000 Individuals Exposed over a Lifetime based on Data from National Cancer Institute Bioassay of Toxaphene for Carcinogenicity[a,b]

	Estimated concentration (ng/l) by tumor type[c,d]		
	H & N	H	T
Mice			
Male, high dose, matched controls	0.417[e]	0.393[e]	
pooled controls	0.409[e]	0.402[e]	
Male, low dose, matched controls	0.502[e]	0.623[e]	
pooled controls	0.467[e]	1.673[e]	
Female, high dose, matched controls	1.996[e]	1.43[e]	
pooled controls	1.996[e]	1.43[e]	
Female, low dose, matched controls	1.84[e]	7.84 (N.S.)	
pooled control	1.84[e]	7.84[e]	
Rats			
Male, high dose, matched controls			108
pooled controls			61.6[e]
Male, low dose, matched controls			237 (N.S.)
pooled controls			55.7 (N.S.)
Female, high dose, matched controls			70.2 (N.S.)
pooled controls			79.9[e]
Female, low dose, matched controls			277 (N.S.)
pooled controls			421 (N.S.)

[a] National Cancer Institute, 1979.
[b] The worksheets and computer output sheets are included in Appendix III of this report.
[c] H & N, hepatocellur carcinoma or neoplastic nodule
H, hepatocellular carcinoma
T, thyroid tumor
[d] N.S. - not significant
[e] tumor incidence significantly greater than controls at p 0.05.

APPENDIX I

Summary and Conclusions Regarding the Carcinogenicity of Toxaphene*

Toxaphene is a mixture of polychlorinated camphenes. It is obtained from camphene by photochemical chlorination which produces a heterogeneous mixture of chemicals (177) containing 67 to 69 percent chlorine. It is structurally related to strobane (polychlorinated terpene), an insecticide (currently not in use) known to induce hepatomas in mice. Toxaphene was found to be mutagenic for Salmonella typhimurium strains TA-98 and TA-100 without metabolic activation.

Two studies, (1) the National Cancer Institute bioassay (dietary study) on toxaphene in mice and rats, and (2) the Bionetics Research Laboratory dietary study (sponsored by Hercules) in mice, have demonstrated that toxaphene is carcinogenic to both mice and rats.

The National Cancer Institute (NCI) dietary study using male and female B6C3F1 mice at doses of 99 and 198 ppm revealed a statistically significant excess of hepatocellular carcinomas in male and female mice at both dose levels.

The Bionetics Research Laboratory study in the same strain (B6C3F1) of male and female mice fed at doses of 7, 20, and 50 ppm in the diet showed a statistically significant excess of hepatocellular tumors (hepatocellular adenoma plus hepatocellular carcinoma) in male mice, but only at the 50 ppm dose.

The National Cancer Institue bioassay study also showed a carcinogenic response induced by toxaphene in both male and female Osborne-Mendel rats only at the high dose level (1,080 ppm), consisting of a statistically significant excess of follicular-cell carcinomas and adenomas of the thyroid.

In summary, carcinogenic responses have been induced in mice and rats by toxaphene. These results, together with the positive mutagenic response, constitute substantial evidence that toxaphene is likely to be a human carcinogen.

The water quality criterion for toxaphene is based on incidence of hepatocellular carcinoma and neoplastic nodules from the low dose $B_6C_3F_1$ male mice bioassay. It is concluded that the water concentration of toxaphene should be less than 4.7×10^{-4} micrograms per liter in order to keep the lifetime cancer risk below 10^{-5}.

*This summary has been prepared by the Carcinogens Assessment Group, EPA, on June 15, 1979.

Derivation of the Water Quality Criterion for Toxaphene

The water quality criterion for toxaphene is derived from the development of hepatocellular carcinomas and neoplastic nodules in the $B_6C_3F_1$ male mice given the low dose of toxaphene in the NCI bioassay study. In that group, a time-weighted average dose of 99 ppm was administered in the diet for 80 weeks and the animals were observed for an additional 10 weeks before terminal sacrifice. The incidence of hepatocellular carcinomas and neoplastic nodules was 7/48 and 40/49 in the pooled control and treated groups, respectively. Assuming a fish bioconcentration factor of 18,000, the criterion is calculated from the following parameters:

$n_t = 40$	$d = 99 \text{ ppm} \times 0.136 = 13.50 \text{ mg/kg/day}$
$N_t = 49$	$w = 0.033 \text{ kg}$
$n_c = 7$	$L = 900 \text{ days}$
$Nc = 48$	$R = 18{,}000$
$Le = 900 \text{ days}$	$F = 0.0187 \text{ kg/day}$
$le = 665 \text{ days}$	

Based on these parameters, the one-hit slope B_H is $4.42 \text{ (mg/kg/day)}^{-1}$. The resulting water concentration of toxaphene calculated to keep the individual risk below 10^{-5} is 4.7×10^{-4} ng/l.

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